TRAMADOLO

Indications

Below, we present the therapeutic indications for tramadol:

1) Tramadol is recommended for use in adult patients and children in the management of acute and chronic pain of various origins and etiologies, ranging from moderate to severe intensity. These include traumatic pain, oncologic-related pain, as well as pain induced by diagnostic and surgical procedures (Agenzia Italiana del Farmaco - AIFA, 2014). The American drug regulatory agency, the Food and Drug Administration (FDA), has approved the use of tramadol only in adult patients. This restriction was further emphasized in 2015 and 2017 due to the widespread use of this drug in the pediatric population (off-label use in the USA) (Food and Drug Administration - FDA, 2015 and 2017). Tramadol can also be combined with paracetamol and is indicated for treatment of mild to moderate acute pain (Agenzia Italiana del Farmaco - AIFA, 2013).

Off-label indications

Below we present the off-label indications for tramadol:

2) Premature ejaculation (Martyn-St. James et al., 2015; Salem et al., 2008).
3) Fibromyalgia (MacLean, Schwartz, 2015).

Dosage

Monotherapy

Below we report the dosage of tramadol in the various therapeutic indications.

The total daily dose of tramadol should not exceed 400 mg (recommended maximum dose).

Analgesia

Oral administration.

Adults and adolescents aged >12 years: initial dose of 50-100 mg of tramadol depending on the pain intensity, or 4-8 administrations (equivalent to 50-100 mg of tramadol; each administration equals 5 drops of solution, i.e., 12.5 mg tramadol) or 20-40 drops/day (equivalent to 50-100 mg of tramadol; 5 drops equal 12.5 mg tramadol) of a solution containing 100 mg/ml of tramadol every 4-6 hours. Maintenance dose: 50-100 mg of tramadol every 4-6 hours.

For moderate pain, 50 mg of tramadol every 4-6 hours (20 drops equal 50 mg). If pain relief is not achieved within 30-60 minutes, administer an additional single dose of 50 mg.

For severe, inadequately controlled pain, administer a single dose of 100 mg.

Dosage should be adjusted based on pain intensity and individual sensitivity. For children aged 12-14 years, the lowest dose is recommended. For chronic pain, a fixed dosage regimen is recommended.

The optimal analgesic effect of tramadol should be achieved through gradual dose escalation to avoid transient side effects. The correct dose for each patient is the minimum effective dose for analgesia that do not produce side effects or produces tolerable side effects within 24 hours.

The analgesic effect lasts 4 to 8 hours, so doses should be administered at intervals of not less than 4 hours.

Extended-Release oral formulations

Adults and adolescents (age >12 years): initial usual dose of 50-100 mg of tramadol twice daily (or 150 mg once daily) in the morning and evening. If pain relief is insufficient, the dose can be increased to 150-200 mg of tramadol twice daily. The interval between administrations can be less than 12 hours but not less than 8 hours. In any case, no more than two doses of extended-release tramadol should be taken within 24 hours.

Extended-release formulations (tablets and hard capsules) should be taken whole with an adequate amount of liquid, regardless of meals. If the patient has difficulty swallowing, capsules can be opened, and the granules inside can be placed on a spoon. Subsequently, the granules should be swallowed with the help of a sufficient amount of liquid to help clean the mouth. Granules should not be chewed or crushed.

Children (age: 1-12 years): 1-2 mg/kg of body weight of tramadol. The dose should not exceed 8 mg tramadol/kg of body weight.

For accurate tramadol dosing in pediatric patients, the most suitable formulation is in drops: 1 drop of 100 mg/mL tramadol solution contains 2.5 mg tramadol. Expressing the dosage in drops, the recommended dosage based on the child's body weight is as follows:

- 10 kg: 4-8 drops
- 15 kg: 6-12 drops
- 20 kg: 8-16 drops
- 30 kg: 12-24 drops
- 45 kg: 18-36 drops

Due to the high dosage, tramadol capsules and tablets are not suitable for children under 12 years old.

Rectal administration.

Adults and children (age >12 years): 100 mg tramadol every 4-6 hours up to a maximum of 400 mg per day.

Parenteral administration.

Adults and adolescents (age >12 years): usual single dose is 50-100 mg of tramadol 3-4 times a day (1-2 mL of injectable solution), every 4-6 hours via slow intravenous (over 2-3 minutes) or intramuscular injection. The injectable solution can also be administered by infusion after dilution, at a rate of 12-24 mg/hour, following an initial intravenous or intramuscular injection of 100 mg.

If pain relief is not achieved within 30-60 minutes after administering 50 mg tramadol, administer an additional single dose of 50 mg. In cases of severe, inadequately controlled pain, administer a dose of 100 mg. Dosage should be adjusted based on pain intensity and individual sensitivity.

The optimal analgesic effect of tramadol should be achieved with a gradual dosage escalation to avoid transient side effects. The correct dose for each patient is the minimum effective dose for analgesia that do not produce side effects or produces tolerable side effects within 24 hours.

The analgesic effect lasts 4 to 8 hours, so doses should be administered at intervals of not less than 4 hours.

Children (age: 1-12 years): initial tramadol dose of 1-2 mg/kg of body weight. The dose can be increased based on the patient's response up to a maximum dose of 8 mg/kg of body weight.

Associations

Analgesic preparations

Tramadol plus paracetamol

Oral administration.

Adults and adolescents (>12 years): initial dose of 75 mg/day (tramadol) plus 650 mg/day (paracetamol). If necessary, the dose can be increased based on therapeutic response and patient tolerance, up to 300 mg/day of tramadol and 2600 mg/day of paracetamol. In case of multiple daily administrations, the interval between successive doses should not be less than 6 hours. To avoid the risk of overdose, other medications containing tramadol or paracetamol should not be taken (including over-the-counter preparations).

Special populations

Elderly patients

In patients under 75 years of age without hepatic or renal impairment, there is no need to adjust the tramadol dose. In patients over 75 years old, tramadol elimination may be slowed down, requiring an extended dosing interval. Therefore, doses exceeding 300 mg/day are not recommended.

Renal dysfunction/dialysis and hepatic failure

In patients with compromised renal or hepatic function, tramadol elimination is slowed down, necessitating consideration of a prolonged dosing interval based on the patient's clinical condition. Since tramadol is eliminated very slowly through hemodialysis or hemofiltration, post-dialytic administration is not necessary. In patients with a reduced glomerular filtration rate (eGFR) of 30% or hepatic impairment, the tramadol dose should not exceed 100 mg per day (50 mg every 12 hours), and extended-release formulations should be avoided (Niscola et al., 2011).

Long-term therapy

Tramadol should not be administered beyond the period absolutely necessary for pain control. Treatment time should be short and intermittent to prevent the risk of developing dependence. If long-term therapy is initiated, the benefits must be carefully evaluated against the associated risks. Patients requiring long-term therapy should be regularly monitored, with temporary discontinuation of the drug if necessary. Sudden discontinuation can lead to withdrawal symptoms.

Contraindications

Below, we report the contraindications for the use of tramadol:

1) Tramadol is contraindicated in cases of hypersensitivity to the active ingredient or opioids.
2) Tramadol is contraindicated in patients experiencing acute intoxication from hypnotics, central nervous system acting analgesics, opioids, psychotropic drugs, or alcohol.
3) Tramadol is contraindicated in patients undergoing treatment with monoamine oxidase inhibitors and within two weeks after discontinuation of such treatment.
4) Tramadol is contraindicated in patients with inadequately controlled epilepsy.
5) Tramadol should not be used for the treatment of withdrawal symptoms from narcotics and other drugs.
6) Tramadol is contraindicated in patients with severe hepatic impairment.
7) Tramadol is contraindicated in patients with respiratory depression, severe bronchial asthma, and uncontrolled hypercapnia (Food and Drug Administration - FDA, 2010).
8) Tramadol in combination with paracetamol (acetaminophen) is contraindicated in patients with severe hemolytic anemia.
9) Tramadol is contraindicated in children under one year of age. The Food and Drug Administration (FDA) has authorized the use of tramadol only in adult patients (its use in the pediatric population is not recommended); FDA explicitly contraindicated the use of the drug in children and adolescents as an analgesic after tonsillectomy and/or adenoidectomy (Food and Drug Administration - FDA, 2017).

Warnings

Respiratory depression: tramadol is not recommended for patients with respiratory insufficiency, for whom a non-opioid analgesic is preferred. The risk of opioid-induced respiratory depression is higher when central nervous system depressant drugs are co-administered and when maximum allowable doses of tramadol are exceeded (Agenzia Italiana del Farmaco - AIFA, 2015; Dayer et al., 1997).

Medical conditions: caution is required when using tramadol in patients with opioid dependence, reduced consciousness due to various causes, seizures, and shock. In cases of head trauma and increased intracranial pressure, tramadol can cause excessive cerebrospinal fluid pressure due to carbon dioxide retention. Tramadol-induced miosis can mask the severity of intracranial pathology (Agenzia Italiana del Farmaco - AIFA, 2014a; Food and Drug Administration - FDA, 2009).

Seizures: tramadol can lead to seizures at therapeutic doses, but the risk increases if the dosage exceeds the recommended amount (>400 mg) or if tramadol is combined with other drugs lowering the seizure threshold (e.g., bupropion). Patients with epilepsy or a history of seizures should carefully evaluate tramadol treatment (Sadock et al., 2015; Sansone, Sansone, 2009). Certain medical conditions can also increase the risk of seizures (head trauma, metabolic disorders, infections, alcohol and drug withdrawal). Naloxone (used in opioid overdose) can also trigger seizures (Food and Drug Administration - FDA, 2009).

Genetic factors: genetic factors influence tramadol analgesic activity. Genetic polymorphisms (genetic variations that result in the coexistence of different phenotypes) of cytochrome P450 2D6, an enzyme that converts tramadol into its active metabolite, may exists. Reduced metabolic activity leads to a lower patient response to tramadol, necessitating a higher dosage to achieve the same effect (Aronson, 2009).

Anesthesia: there is no information available regarding the safe use of tramadol in anesthesia (Agenzia Italiana del Farmaco - AIFA, 2015). A study observed tramadol causing awakening in 65% of patients anesthetized with nitrous oxide and enflurane during surgery (Lehmann et al., 1985).

Combination with agonists and antagonists: combining opioid receptor agonists and antagonists (e.g., buprenorphine, pentazocine, nalbuphine) can reduce the efficacy of pure agonists (Agenzia Italiana del Farmaco - AIFA, 2013a).

Hepatic and renal failure: tramadol and its active metabolite excretion is slowed in patients with hepatic and renal failure, leading to increased drug half-life. Dosage reduction is necessary for patients with creatinine clearance >30 ml/min and hepatic cirrhosis (Food and Drug Administration - FDA, 2009).

Diabetic patients: tramadol, according to what emerged from a pharmacovigilance study, has been associated with a 52% higher risk of hypoglycemia and hospitalization for hypoglycemia compared to codeine. Hypoglycemia occured within

10 days of starting tramadol therapy, even in the absence of risk factors such as diabetes mellitus (Fournier et al., 2015). The association between tramadol and hypoglycemia was also confirmed by a retrospective analysis of data collected by the U.S. Food and Drug Administration from January 2004 to March 2019 in the Adverse Effect Reporting System (FAERS) and the Adverse Event Reporting System (AERS). In this analysis, the risk of tramadol-induced hypoglycemia was 10 times higher than with any other opioid; only methadone shared this effect with tramadol, and the mechanism has not yet been identified (Makunts et al., 2019).

Children: the U.S. regulatory agency (Food and Drug Administration) has not approved the use of tramadol in children and adolescents under the age of 18 (there is no pediatric-friendly liquid formulation available in the U.S.). However, tramadol is widely used off-label in the pediatric population. This led the FDA to review available literature to assess tramadol's safety for this patient category, especially regarding the risk of respiratory compromise, which appears to increase in children undergoing tonsil and adenoid removal surgeries. The FDA's evaluation led to contraindicating the drug in children and adolescents undergoing tonsil and/or adenoid removal surgeries and not recommending its use in obese adolescents or those with conditions such as obstructive sleep apnea or severe lung diseases that may increase the risk of respiratory problems (Food and Drug Administration - FDA, 2017). The FDA also considered the issue of genetic variations (polymorphisms) among individuals, including children, which affect tramadol metabolism rate and the quantity of pharmacologically active metabolite produced in this process. Specifically, if metabolism rate increases (ultra-rapid metabolizers), levels of the active metabolite can exceed normal values, compromising respiratory function (Food and Drug Administration - FDA, 2015). Through the U.S. pharmacovigilance system (FAERS, FDA's Adverse Event Reporting System), the FDA identified 9 cases of severe respiratory problems following tramadol use in the pediatric population (January 1969-March 2016). Most cases occurred in children under 12 years old after taking a single dose of the drug; three cases were fatal (Food and Drug Administration - FDA, 2017).

Hypersensitivity reactions: tramadol can induce hypersensitivity reactions, often after the first dose (anaphylactoid reaction), which can also be fatal. Urticaria, itching, bronchospasm, angioedema, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) can be triggered by tramadol (Food and Drug Administration - FDA, 2009).

Drowsiness: tramadol can induce side effects such as drowsiness and dizziness, especially when combined with central nervous system depressant drugs or alcohol. Tramadol can impair driving ability (Agenzia Italiana del Farmaco - AIFA, 2014a; Dayer et al., 1997).

Narcotic and other drug withdrawal: tramadol is not suitable as a substitution treatment in opioid addicts to alleviate morphine withdrawal symptoms (Agenzia Italiana del Farmaco - AIFA, 2014a).

Paracetamol overdose: some medications contain fixed-dose combination of tramadol and paracetamol (acetaminophen). Paracetamol overdose is more likely in

patients with non-cirrhotic alcoholic liver disease. In patients with severe hepatic impairment, paracetamol is contraindicated due to potential hepatic toxicity. For patients with moderate hepatic failure, extending the dosing interval should be considered (Agenzia Italiana del Farmaco - AIFA, 2015).

Suicidal ideation: for individuals with suicidal ideation, depression, or those taking antidepressants, anxiolytics, or excessive alcohol, non-narcotic analgesics are preferable (Food and Drug Administration - FDA, 2009).

Withdrawal symptoms: withdrawal symptoms can occur even with short-term and therapeutic doses of tramadol, so gradual dosage reduction before discontinuation is advisable. Withdrawal symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor, gastrointestinal symptoms, and, more rarely, panic attacks, severe anxiety, hallucinations, paresthesias, tinnitus, involving the central nervous system (Agenzia Italiana del Farmaco - AIFA, 2015; Senay et al., 2003).

Dependence: tramadol, less frequently than other opioid medications, leads to tolerance and dependence, especially with long-term therapy. In patients addicted to opioids and prone to drug abuse, tramadol should be administered for a short period under strict medical supervision (Agenzia Italiana del Farmaco - AIFA, 2014a; Naslund, Dahlqvist, 2003).

Fertility: some clinical studies suggest potential fertility impairment in women at high tramadol doses (Agenzia Italiana del Farmaco - AIFA 2014a).

Pregnancy: the safety of tramadol during pregnancy has not been established. Some studies indicate that tramadol, at very high doses, affects organ development, ossification process, and neonatal mortality. Tramadol crosses the placental barrier and chronic use can lead to neonatal withdrawal syndrome. Tramadol may also influence respiratory rate, although there is no clinical relevance to this effect (Agenzia Italiana del Farmaco - AIFA, 2014a; De Wit, Koomen-Botman, 2013).

Lactation: tramadol therapy is not recommended in breastfeeding women because tramadol passes into breast milk in small quantities (0.1%) (Marcus, Bain, 2009; Food and Drug Administration – FDA, 2017).

Interactions

Antidepressants (selective serotonin reuptake inhibitors SSRI, serotonin-norepinephrine reuptake inhibitors SNRI, MAO inhibitors, tricyclic antidepressants, mirtazapine): the combination of tramadol with antidepressant medications increases the risk of serotonin syndrome and seizures (Sansone, Sansone, 2007).

Antidepressants and tramadol, through different mechanisms, enhance serotonin concentration in the synaptic space, between neurons, thereby potentiating serotoninergic transmission. Episodes of serotonin syndrome (agitation, confusion, tremors, diaphoresis, myoclonus, hyperreflexia, mydriasis, tachycardia, fever) have been reported with tramadol combined with mirtazapine and venlafaxine (Houlihan, 2004). Coma, seizures, hypotension followed by ventricular tachycardia leading to cardiac arrest due to asystole and refractory shock have been reported in tramadol intoxication in combination with central nervous system depressants such as hydroxyzine, gabapentin, and clonazepam (Daubin et al., 2007).

Non-steroidal anti-inflammatory drugs (NSAIDs): tramadol combined with NSAIDs provides complete analgesia as its action occurs at all levels (Novelli et al., 1999).

In vivo (rats) studies have shown NSAIDs antagonizing tramadol-induced constipation in the gastrointestinal tract (Planas et al., 2003).

Atomoxetine: increases the risk of seizures according to an unknown mechanism (Karalliedde et al., 2010).

Bupropion: lowers seizure threshold, increasing the risk of seizures in tramadol therapy (Sadock et al., 2015).

Carbamazepine: carbamazepine is a potent inducer of cytochrome enzyme CYP3A4, potentially inducing tramadol metabolism, reducing its plasma levels. Considering an alternative therapy to carbamazepine may reduce the risk of reduced analgesic effect of tramadol. However this interaction does not appear to be clinically significant presently (Agenzia Italiana del Farmaco - AIFA, 2014a).

Quinine: quinine inhibits cytochrome P450 2D6 enzyme activity, leading to increased tramadol plasma concentration and hence its analgesic activity. Sedative effects need monitoring due to the risk of narcosis (Karalliedde et al., 2010).

Clarithromycin: visual and auditory hallucinations have been reported in association with tramadol (case reports) (Kovacs, Peter, 2010). Both drugs can induce hallucinations, but co-administration might increase the risk due to pharmacometabolic effects. Clarithromycin inhibits cytochrome enzyme CYP3A4, responsible for tramadol metabolism. The combination of the two dugs likely leads to increased tramadol concentration levels, intensifying observed effects.

Cimetidine: can cause an increase in tramadol plasma levels by inhibiting its metabolism mediated by cytochrome P450 2D6 activity (Karalliedde et al., 2010).

Digoxin: tramadol may lead to an increase in digoxin concentration through an unknown mechanism. Careful monitoring of digoxin levels is crucial, and if necessary, dose reduction is recommended due to digoxin's narrow therapeutic window (a pharmacological parameter indicating the safety of a drug) and high potential for toxicity (Karalliedde et al., 2010).

Erythromycin and ketoconazole: inhibit metabolic reactions mediated by cytochrome P450 3A4, possibly increasing tramadol serum levels through pharmacometabolic inhibition. The clinical relevance of this pharmacological interaction is unknown (Agenzia Italiana del Farmaco - AIFA, 2015).

Antiemetic drugs (ondansetron, droperidol): these drugs antagonize the serotonin 5-HT3 receptor, a neurotransmitter involved in modulating pain sensitivity pathways (nociception). Co-administration of ondansetron and tramadol, whose central analgesic activity partly depends on increased serotoninergic transmission, can reduce tramadol's analgesic activity. Consequently, higher doses of the analgesic are needed for pain control (Arcioni et al., 2002). Additionally, both antiemetic drugs antagonize tramadol's inhibitory effect on intestinal transit (preclinical data, in vivo) (Dursteler et al., 2006).

Drugs lowering seizure threshold (selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, central analgesics, local anesthetics, tetrahydrocannabinol, mirtazapine): facilitate the onset of seizures (Agenzia Italiana del Farmaco - AIFA, 2015).

Central nervous system depressant drugs (opioid derivatives, including cough medicines and replacement therapies, barbiturates, benzodiazepines, other anxiolytics and hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally acting antihypertensives, thalidomide, baclofen) and alcohol: these drugs increase sedative effects on the central nervous system and tramadol's respiratory depression. Driving attention might be compromised (Agenzia Italiana del Farmaco - AIFA, 2015; Dayer et al., 1997).

Fluoxetine, paroxetine: fluoxetine and paroxetine are specific enzymatic inhibitors of cytochrome P450 2D6, the enzyme responsible for metabolizing tramadol into its active metabolite. Reduced production of this metabolite leads to a decrease in analgesic effects (Laugesen et al., 2005; Lynch, Price, 2007).

Protease inhibitors (indinavir, saquinavir, ritonavir with or without lopinavir): these inhibit the activity of cytochrome P450 2D6 and can therefore potentially lead to tramadol's side effects (Karalliedde et al., 2010).

MAO Inhibitors: historical observations indicate that monoamine oxidase inhibitors increase the toxicity of analgesic drugs (meperidine (or petidine), morphine, pentazocine, phenazocine), associated with increased serotonin levels in the brain (Browne, Linter, 1987; Rogers, Thornton, 1969). Therefore, this class of antidepressants is contraindicated in combination with tramadol. Tramadol should be administered no sooner than two weeks after discontinuing these medications (Agenzia Italiana del Farmaco - AIFA, 2015).

Methadone: inhibits tramadol metabolism mediated by cytochrome P450 2D6, transforming tramadol into its active metabolite, O-demethylated (M1). Methadone partially reduces tramadol activity, which is partly mediated by its metabolite (Coller et al., 2012).

Rasagiline, selegiline (anti-Parkinson drugs): the combination of these drugs with meperidine has been linked to hyperpyrexia (body temperature above 40.5 °C) through an unknown mechanism. Similar effects are considered likely in combination with tramadol due to its resemblance to meperidine (Karalliedde et al., 2010).

Rifampicin: induces tramadol metabolism, causing changes in pharmacokinetic parameters. The AUC (area under the concentration-time) of tramadol and its active metabolite decreases (by 43% and 58% respectively for intravenous administration; 59% and 54% following oral administration). Bioavailability decreases from 66% to 49% after rifampicin administration (Saarikoski et al., 2013).

Ticlopidine: is a potent inhibitor of cytochrome P450 2B6, which slows tramadol and its active metabolite elimination. Tramadol pharmacokinetic parameters increase, while those of its metabolite decrease (Hagelberg et al., 2013).

Triptans: co-administration of tramadol with triptans enhances serotonin transmission, increasing the risk of serotonin syndrome (Food and Drug Administration - FDA, 2009).

Warfarin: co-administration of tramadol with warfarin elevates the International Normalized Ratio (INR), necessitating a reduction in warfarin dosage (approximately 25-30%) and continuous INR monitoring during the week following tramadol initiation (Dumo, Kielbasa, 2006).

Side effects

The side effects of tramadol are typical of opioid analgesics: nausea, vomiting, urinary retention, drowsiness, constipation, dry mouth, immunosuppressive effects, dysphoria, and constipation. Nausea, dizziness, and drowsiness are the most common side effects, affecting over 10% of treated patients.

Compared to equipotent doses of other opioids, the side effects of tramadol are milder in intensity and frequency, making it more tolerable. Tramadol treatment has a low potential for abuse and dependence, lacks tolerance development (where the effect diminishes over time, requiring higher doses for the same effect), and rarely leads to respiratory depression and cardiovascular events due to its unique mechanism of action (Agenzia Italiana del Farmaco - AIFA, 2015; Dayer et al., 1997; Novelli et al., 1999; Scott, Perry, 2000). Gastrointestinal motility effects are also reduced (Agenzia Italiana del Farmaco - AIFA, 2014).

Side effects are dose-dependent, with lower initial doses enhancing tolerability (Dayer et al., 1997). Extended-release oral tramadol formulations further reduce adverse effects (Aronson, 2009).

Following discontinuation of tramadol treatment or dose reduction, withdrawal symptoms may occur, some typical of opioids and others are not commonly observed with opioid discontinuation. Atypical symptoms include hallucinations, paranoia, severe anxiety, panic attacks, confusion, and tingling extremities (Senay et al., 2003).

Allergic: immunosuppressive effects, allergic reactions (bronchospasm, dyspnea, wheezing, angioedema), anaphylaxis (rare). The risk of anaphylactic reactions increases in patients with previous reactions similar to codeine and other opioids (Food and Drug Administration - FDA, 2009).

Cardiovascular: palpitations, tachycardia. Postural hypotension or cardiovascular collapse, especially during physical stress and intravenous administration. Rarely, bradycardia, increased blood pressure, and hot flashes have been recorded.

Coagulation disorders: cases of blood dyscrasia (thrombocytopenia, agranulocytosis) have been reported following tramadol and paracetamol co-administration (Agenzia Italiana del Farmaco - AIFA, 2013).

Eye: miosis, mydriasis, blurred vision.

Gastrointestinal: nausea, constipation, vomiting, dry mouth, increased gastric pH, gastric emptying inhibition, and gastrointestinal irritation (bloating, gastric tension), diarrhea (Aronson, 2009).

Genitourinary: dysuria, urinary retention.

Liver/biliary: elevation of liver enzyme values.

Metabolic disorders: altered appetite, hypoglycemia.

Tramadol has been associated with an increased risk of hypoglycemia, which, if untreated, can lead to a higher risk of falls, neurocognitive and visual impairments. From available data, tramadol is associated with a 10-fold increased risk of hypoglycemia compared to all other opioids; only methadone was found to have a similar effect. Diabetics and pre-diabetic patients are the most exposed category, but this adverse effect has also been observed in the absence of risk factors for diabetes (Fournier et al., 2015; Makuntus et al., 2019).

Musculoskeletal: muscle weakness.

Nervous system: dizziness, drowsiness, and headaches. Less common effects include language disorders, paresthesia, tremors, seizures, involuntary muscle contractions, motor incoordination, syncope, serotonin syndrome; confusion, sleep disturbances, visual and auditory hallucinations, delirium, anxiety, nightmares (Aronson, 2009), mood changes (euphoria, dysphoria), sensory and cognitive impairments; dependence, and withdrawal syndrome upon discontinuation of therapy.

Seizures and serotonin syndrome occur more frequent with tramadol overdose or in combination with antidepressants (Sansone, Sansone, 2009).

Seizures occur in less than 1% of patients on tramadol monotherapy, but the risk increases 2-6 times when tramadol is combined with other drugs, comorbidities, or in patient with a history of seizures. Individuals aged 25-54, with alcohol abuse, heart attack, or head trauma history are particularly affected (Aronson, 2009; Sansone, Sansone, 2007).

Seizures often manifest within 24 hours of tramadol ingestion, more commonly in young, long-term tramadol users who also consume alcohol (Jovanovic-Cupi et al., 2006).

Seizures are more commonly associated with male patients who chronically use tramadol, attempted suicide with tramadol, intentional misuse of tramadol, and patients with tachycardia (HR >100 beats/minute; HR = Heart rate) (Marquardt et al., 2005). Symptoms like tachycardia and mydriasis predict seizure risk (Tashakori, Afshari, 2010).

Serotonin syndrome is a pathological condition resulting from excessive stimulation of serotonin receptors in the central and peripheral nervous system, due to various drugs acting on the serotonin system. Tramadol, especially in combination with antidepressants that potentiate this activity through different mechanisms, can induce serotonin syndrome (tramadol inhibits serotonin reuptake in the raphe nucleus, a brain region involved in REM sleep phases and pain modulation). Several pharmacological agents or substances of abuse that increase serotonin transmission can cause serotonin syndrome (buspirone, ergot alkaloids, amphetamines, cocaine). Serotonin syndrome presents characteristic symptoms related to neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia, rigidity), excessive autonomic nervous system activity (sweating, fever, tachycardia, tachypnea), and altered mental state (agitation, confusion) (Benzon et al., 2013; Sansone, Sansone, 2007).

Respiratory: respiratory depression, dyspnea, worsening of asthma.

At therapeutic doses (1 mg/kg), tramadol causes less respiratory depression than other opioids, making it suitable for pediatric use, orally or intravenously (Ivani, 2000). The risk of respiratory depression increases with exceeding recommended doses or combining tramadol with other central depressant substances.

Skin: hyperhidrosis, itching, rash (rare), and urticaria. Subcutaneous nodules, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported (Aronson, 2009; Mockenhaupt et al., 2008). Cases of paracetamol (acetaminophen) hypersensitivity with skin rash and very rare severe skin reactions have occurred following tramadol and paracetamol co-administration (Agenzia Italiana del Farmaco - AIFA, 2013).

Toxicity

Overdose: the higher tolerance of tramadol compared to other drugs in the same therapeutic class has made it widely prescribed medication. However, severe complications can arise in cases of overdose (the recommended maximum daily dose is 400 mg per day) (De Backer et al., 2010).

Overdose symptoms are similar to those induced by other opioid analgesics and include: miosis, vomiting, cardiovascular collapse, impaired consciousness up to coma, seizures, respiratory depression leading to respiratory arrest (Agenzia Italiana del Farmaco - AIFA, 2015).

Tramadol can cause seizures and serotonin syndrome, two significant adverse events that mainly occur in cases of overdose and polytherapy with other drugs (especially antidepressants). Risk factors for these events include age, epilepsy, and neurological disorders.

In a study enrolled 126 patients, 87 of whom were on tramadol monotherapy, the following tramadol overdose symptoms were observed: lethargy (30%), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), hypertension (5%), coma (5%), respiratory depression (2%). All seizure episodes were of short duration, and all symptoms were recorded within 4 hours of ingestion. Effects such as seizures, agitation, hypertension, tachycardia occurred at doses >500 mg, while coma and respiratory depression occurred at doses >800 mg, indicating a more severe condition. No cases of arrhythmia or serious cardiovascular events were recorded, but rather a serious neurological compromise.

Various drugs were used to counteract these effects: diazepam, nifedipine, lorazepam, and phenytoin. Naloxone was effective against sedation and apnea in some cases (Spiller et al., 1997).

There have been reported cases of death due to accidental tramadol intoxication, caused by severe liver failure and subsequent fulminant cirrhosis. Post-mortem toxicological analyses found plasma concentrations of tramadol higher than therapeutic levels, confirming the link between the fatal event and tramadol use. These cases are among the few caused by tramadol in monotherapy (De Decker et al., 2008; Loughrey et al., 2003).

In one study, tramadol at concentrations of 30, 100, 300 micrometers, which are recorded at doses higher than therapeutic, inhibited myometrial contractility stimulated by potassium chloride (Shah et al., 2013).

Emergency treatments for tramadol intoxication aim to restore cardiac and respiratory function, which can be compromised. For respiratory depression, it is crucial to maintain open airways (aspiration) and, if necessary, administer naloxone as an antidote, although it only partially antagonizes tramadol activity. Naloxone does not act against seizures, so intravenous diazepam should be administered (Ivani, 2000).

Hemodialysis and hemofiltration are not measures to adopt because tramadol is eliminated only to a small amount through these routes (7%).

If tramadol is ingested orally, gastric lavage and activated charcoal are effective within the first two hours after ingestion. Only if the ingested amounts are very high or if the formulation is extended-release, the intervention's effectiveness can extend beyond two hours.

In case of combined intake of tramadol and paracetamol, symptoms of paracetamol overdose may occur. After 24 hours, pallor, nausea, vomiting, anorexia, abdominal pain can occur, and within 48 hours, liver damage may manifest, worsening into encephalopathy, potentially leading to death. Hepatic damage in adults occurs after ingestion of paracetamol doses of ≥7.5-10 g, where excessive amounts of toxic metabolites are formed, partially neutralized by glutathione. Alterations in glucose metabolism, metabolic acidosis, acute renal failure with tubular necrosis can occur. Cases of arrhythmia and pancreatitis have been reported. The risk of liver toxicity increases for patients with liver diseases or those consuming alcohol along with paracetamol (Agenzia Italiana del Farmaco - AIFA, 2015; Proudfoot, Wright, 1970; Rumack, 1983).

Pharmacology

Tramadol is a centrally acting opioid analgesic drug, structurally related to codeine and morphine.

Tramadol exists as two enantiomers, each operating through distinct mechanisms, conferring a unique pharmacodynamic profile to the molecule. Tramadol exerts its activity on pain transmission not only through an opioid mechanism but also via a non-opioid mechanism involving biogenic amines, synergistic with the typical opioid pathways.

The opioid mechanism of tramadol is mediated by its binding to the mu receptor, with an affinity 10 times lower than codeine, 60 times lower than dextropropoxyphene, and 6000 times lower than morphine. However, the active metabolite of tramadol, O-desmethyltramadol (M1), has a significantly higher affinity than tramadol itself (200 times) and a potency six times greater. The dextro (+) enantiomer binds to opioid receptors and inhibits serotonin reuptake, while the levo (-) enantiomer inhibits norepinephrine reuptake, influencing the adrenergic system. These complementary mechanisms translate into enhanced inhibitory effects on pain transmission at the spinal cord level, thereby augmenting the analgesic effect of tramadol. Specifically, descending inhibitory pathways projecting from the brain to the spinal cord are involved. Activation of these pathways stimulates interneurons that inhibit pain transmission at the spinal level.

Since tramadol shares some of its mechanism of action with antidepressant drugs (inhibitory effect on serotonin and adrenaline reuptake) and also structurally resembles one of these drugs (venlafaxine), it shares certain pharmacological effects. Antidepressants, by enhancing biogenic amine action, also exert analgesic activity (Benzon et al., 2013; Gobel, Stadler, 1997; Grond, Sablotzki, 2004; Sansone, Sansone, 2009).

The antinociceptive activity of tramadol is mediated by 5-HT1A the serotonin receptor but not the 5-HT1B receptor. The 5-HT1A receptor is also involved in modulating neuropathic pain and the antidepressant effects of tramadol (Berrocoso et al., 2006; Berrocoso et al., 2007).

The analgesic effect of tramadol can be enhanced by combining it with a non-opioid analgesic, with its potency being 10% of that of morphine when administered parenterally.

Tramadol is indicated in patients with compromised cardiac and pulmonary function, post-thoracic or upper abdominal surgeries, and in patients for whom non-opioid analgesics are contraindicated. It is also preferred over nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with gastrointestinal and renal disorders since tramadol does not cause gastrointestinal bleeding and renal toxicity by interfering with prostaglandin production (Gullo, 2003).

Tramadol effectively alleviates moderate to severe pain of various origins, including post-operative pain, trauma-induced pain, renal and biliary colic, neuropathic pain, lower back pain, and osteoarthritis (Grond, Sablotzki, 2004).

Tramadol is not used as an adjunct in general anesthesia due to insufficient sedative effects (Lehmann, 1997).

Tramadol has been associated with local anesthetic effects, anti-inflammatory activity in rat experimental models, reduction of substance P levels in human synovial fluid, and agonistic activity on the alpha2-adrenergic receptor (Benzon et al., 2013).

Additionally, tramadol exhibits antitussive action, the potency of which depends on its structure and that of its metabolite (Hennies et al., 1988).

Tramadol with NSAIDs

Tramadol and nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects through different yet complementary mechanisms. Tramadol acts on pain descending pathways, while NSAIDs target the pain source. Their combination (e.g., tramadol + paracetamol) provides complete analgesia, operating at various levels (Novelli et al., 1999).

Tramadol with paracetamol

Tramadol has an additive effect with paracetamol; paracetamol induces initial analgesia within 20 minutes of administration, which is subsequently prolonged compared to tramadol monotherapy. Additionally, the combination reduces the risk of liver toxicity as both drugs are present in smaller quantities. The therapeutic efficacy of tramadol-paracetamol combination is comparable to codeine-paracetamol for chronic osteoarthritis therapy, with greater tolerability (Benzon et al., 2013).

Trauma-induced pain

In a double-blind randomized study, tramadol activity was compared to ketorolac (an NSAID) for treating severe pain associated with bone fractures in children. Both drugs, administered sublingually, provided similar pain relief (Neri et al., 2013).

Oncologic Pain

Tramadol is effective in treating oncologic pain of varying severity, from moderate to severe. In cases of metastatic malignant tumors, tramadol significantly reduced pain intensity (numeric pain scale evaluation: reduced from 6.75 to 3.03; $p < 0.001$), increased pain relief from 25.75 to 71.81; $p < 0.001$), and improved sleep quality (impact of pain reduced from 51.51% to 10.61%; $p < 0.001$). Moreover, 60% of patients reported mild pain (Bosnjak et al., 2007). Tramadol has been found to be effective in cases where non-opioid analgesics were ineffective. In patients with moderate to severe oncologic pain unresponsive to treatment with naproxen 1g/day, extended-release tramadol was effective in two-thirds of patients both after the first dose and as a long-term treatment. The number of patients experiencing relief

increased from 43% to 71% from the first to the sixth week, and opioid-typical side effects diminished during treatment (Petzke et al., 2001).

Post-Operative Pain

In numerous studies, tramadol administered orally and parenterally has demonstrated significant efficacy in managing moderate to severe pain associated with surgical procedures. Tramadol provides pain relief in both children and adults, comparable to morphine and alfentanil, and superior to pentazocine, and other opioid drugs. Unlike other opioids, tramadol does not significantly compromise respiratory function, making it particularly useful for patients with compromised breathing such as the elderly, smokers, obese individuals, and those with reduced hepatic and renal function (Scott, Perry, 2000). However, the U.S. Food and Drug Administration (FDA) has contraindicated tramadol for pain relief in pediatric patients undergoing tonsillectomy and/or adenoidectomy due to the risk of respiratory problems (Food and Drug Administration - FDA, 2017).

Tramadol is more potent than nonsteroidal anti-inflammatory drugs (NSAIDs) for this therapeutic indication (Lehmann, 1997) and can be a viable therapeutic alternative for patients for whom NSAIDs are not recommended (Scott, Perry, 2000). Conversely, when combined with NSAIDs, tramadol can be administered at lower doses, causing fewer side effects.

Some studies have reported an effective tramadol dose of 50 mg administered intravenously, followed by a second dose after 30 minutes if necessary, for acute pain. Higher doses are required for more severe pain. Tramadol is considered a first-line treatment for post-operative pain relief due to its good tolerance and rare side effects such as respiratory and cardiac depression, dizziness, drowsiness, potential for dependence and abuse compared to morphine and meperidine, administered at equivalent dosage (Lehmann, 1997).

Opioid withdrawal

Tramadol has been considered a potential opioid-like agent for treating opioid withdrawal symptoms. In a study involving heroin-abusing patients, tramadol demonstrated efficacy comparable to buprenorphine in alleviating mild to moderate symptoms resulting from heroin discontinuation (Tamaskar et al., 2003).

Depression

Tramadol exerts an antidepressant effect by modulating the 5-HT1A serotonin receptor. It has been observed that an antagonist of this receptor (WAY 100635) significantly reduces this effect (Berrocoso et al., 2006).

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a global incidence of 2-3%. Patients with OCD are plagued by recurrent, anxiety-inducing

obsessive thoughts that drive repetitive and stereotyped compulsive behaviors to alleviate them, interfering with daily practical activities.

Tramadol is considered a pharmacological agent that enhances the action of antidepressant drugs targeting the serotonin system in patients with obsessive-compulsive disorder who respond less to these medications. Tramadol has been shown to be effective in reducing the symptoms characteristic of obsessive-compulsive disorder by a mechanism not fully understood, but tramadol-induced activation of serotoninergic neurons may inhibit glutamate release, an excitatory neurotransmitter in the cortex (Pittenger et al., 2005).

Premature Ejaculation

Premature ejaculation is a widespread male sexual dysfunction, affecting 20-30% of men, significantly impacting their quality of life (Bar-Or et al., 2012). Tramadol is used off-label for premature ejaculation treatment. Several randomized clinical trials have been conducted to assess its potential pharmacological role.

To test tramadol's efficacy, the intravaginal ejaculation latency time (IELT) was used as a parameter, showing increased IELT after tramadol treatment compared to placebo and other treatments such as paroxetine, sildenafil, lidocaine gel, and behavioral therapy. However, high variability in study results and various side effects associated with tramadol, such as erectile dysfunction, constipation, nausea, headache, drowsiness, dry mouth, itching, and vomiting, have been reported (Martyn-st. James et al., 2015).

In a study involving patients with premature ejaculation, characterized by IELT values <2 minutes in at least 80% of episodes, tramadol significantly increased this parameter from 1.17 +/- 0.30 minutes (before treatment) to 7.37 +/- 2.53 minutes (at the end of treatment), compared to placebo (Salem et al., 2008).

This effect was also observed in another clinical study, where tramadol improved premature ejaculation profile (PEP), a parameter used to assess the dysfunction (Bar-Or et al., 2012).

Based on the clinical trial results (improvement in intravaginal ejaculation latency time, control of the process, and subjective satisfaction), tramadol could be considered an alternative therapeutic option to serotonin reuptake inhibitors like dapoxetine (Kaynar et al., 2012).

Migraine

Intramuscular tramadol has been considered a potential drug for relieving acute migraine attacks. In a prospective randomized study, patients (n =17) received 100 mg tramadol intravenously (30-minute infusion) or 100 mg placebo solution. Treatment response, assessed by a decrease in scores on Visual Analog Scale (VAS) and 4-point Verbal Scale (FPVS), was significantly higher in the tramadol-treated group, which was well-tolerated by patients (Alemdar et al., 2007).

Tramadol efficacy in acute migraine attacks was also compared to diclofenac, a nonsteroidal anti-inflammatory drug, in a prospective double-blind randomized study. Patients with acute migraine attacks were treated with either 100 mg of tramadol (n =20) or 75 mg of diclofenac (n =20) intramuscularly. Symptom severity was assessed at 30, 60, 90, and 120 minutes using a scale, along with possible adverse events. Patients were also monitored for recurrence after 48 hours.. Both treatments showed no significant differences in pain relief, adverse effects, or recurrence of attacks after 48 hours (Engindeniz et al., 2005).

One study involved adult migraine patients with moderate to severe pain who were treated with a dose of tramadol/paracetamol or placebo of 75 mg/650 mg. Tramadol, in combination with paracetamol, was effective in reducing pain and symptoms associated with migraines (Silberstein et al., 2005).

Neuropathic Pain

Tramadol has shown significant efficacy compared to placebo in relieving neuropathic pain, both physically and psychologically. Some adverse effects, such as nausea, headache, constipation, and drowsiness, have been reported, but the drug's tolerability has been considered generally good for this indication (Harati et al., 1998; Hollingshead et al., 2006). In a rat model of neuropathic pain induced by partial sciatic nerve ligation (PSL), tramadol orally strongly counteracted the induced allodynia in a dose-dependent manner (Kaneko et al., 2014).

Tramadol analgesic effect on neuropathic pain is attributed to its specific mechanism of action, involving weak opioid receptor interaction and potentiation of the monoaminergic system. Serotonin 5HT-1A receptors, in particular, are implicated in the antinociceptive action, along with opioid receptors. Antagonist drugs for these receptors, combined with tramadol, represent potential agents to enhance the action of tramadol in neuropathic pain (Berrocoso et al., 2007).

Fibromyalgia

The use of tramadol for fibromyalgia has not be approved (off-label use), but there is scientific evidence supporting its effectiveness as a second-line treatment for more resistant cases (MacLean, Schwartz, 2015). Tramadol analgesic effect has been studied in rat models of reserpine-induced fibromyalgia (RIM). Tramadol reduced allodynia in rats induced by reserpine. The effect of tramadol was partially antagonized by naloxone, indicating mediation through an opioid receptor mechanism (Kaneko et al., 2014).

Post-herpetic neuralgia

Antidepressants are often used in post-herpetic neuralgia treatment, sometimes in combination with neuroleptics and, occasionally, opioids to enhance analgesic action. In a clinical study, tramadol use for post-herpetic neuralgia was compared to the antidepressant clomipramine, with or without the neuroleptic levomepromazine. Patients received personalized doses up to a maximum of tramadol 600 mg and clomipramine 100 mg, with or without levomepromazine 100 mg. Pain relief was

comparable in both treatment groups, with similar tolerability. Tramadol also did not alter the psycho-physical conditions of patients, making it an alternative therapeutic option for patients for whom antidepressants are contraindicated (patients with cardiovascular diseases, mainly ≥65 years old) (opioids and tramadol are used as second- or third-line drugs in post-herpetic neuralgia treatment) (Gobel, Stadler, 1997; Harden et al., 2013).

Restless legs syndrome

Tramadol is used in the treatment of restless legs syndrome; other therapeutic options include carbidopa/levodopa, pramipexole, ropinirole, oxycodone, methadone, and codeine (Ferini-Strambi, Marelli, 2014). Dopaminergic system-active drugs are the first choice in treatment.

In an open-label study, tramadol administered at a dose of 50-150 mg/day was associated with a significant improvement in symptoms in 10 out of 12 patients, a mild improvement in 1 patient, and no improvement in 1 patient. No patients experienced side effects or tolerance (the need to increase the drug dose to achieve the same pharmacological effect) (Lauerma, Markkula, 1999).

Pharmacokinetics

Tramadol possesses a lipophilic structure analogous to codeine.

Chemically, tramadol exists as a racemic mixture of two enantiomers, (+) tramadol (enantiomer R,R) and (-) tramadol (enantiomer S,S), which are identical but non-superimposable molecules.

When orally administered, tramadol is absorbed nearly completely from the gastrointestinal tract within 15-45 minutes, reaching peak plasma concentration in 2 hours, and is rapidly distributed throughout the body. Its bioavailability after a single dose is approximately 70%; about 30% undergoes first-pass metabolism and does not reach the bloodstream. However, after multiple administrations, tramadol bioavailability reaches 100%. Tramadol controlled-release pharmaceutical form releases the active ingredient over 12 hours, with a peak concentration 8Cmax, maximum concentration achieved) occulting after 4.9 hours, and a bioavailability of 87-95%. Oral liquid forms (oral solution drops) are rapidly absorbed, reaching peak concentration in about 1 hour.

Intramuscularly tramadol exhibits 100% bioavailability, with a plasma peak achieved in 45 minutes. The average duration of action for tramadol is 6 hours, and its analgesic effect becomes evident approximately 10-20 minutes after administration (Agenzia Italiana del Farmaco - AIFA, 2014; Agenzia Italiana del Farmaco - AIFA, 2014a; Caraceni et al., 2007; Grond, Sablotzki, 2004; Gullo, 2003). Intramuscular administration of tramadol provides a gradual therapeutic effect, while intravenous administration results in immediate analgesia with fluctuating plasma concentrations, requiring close monitoring. Continuous intravenous tramadol delivery devices have resolved this issue by ensuring constant tramadol levels and eliminating interindividual differences in pharmacokinetics and pharmacodynamics (Gullo, 2003).

Tramadol undergoes hepatic phase I metabolism through O- and N-demethylation reactions, yielding five compounds: mono-O-demethyl-tramadol (M1), mono-N-demethyl-tramadol (M2), di-N-demethyl-tramadol (M3), tri-N,O-demethyl-tramadol (M4), and di-N,O-demethyl-tramadol (M5). O-demethylation is catalyzed by cytochrome P450 2D6 enzymes, while N-demethylation is mediated by cytochrome 2B6 and 3A4.

Cytochrome P450 enzymes exhibit genetic polymorphisms, causing variability in tramadol's pharmacokinetic profile. For instance, different cytochrome P450 2D6 genotypes (which determine the enzyme's activity) influence tramadol and its O-demethylated metabolite concentrations and, consequently, its analgesic efficacy (Stamar et al., 2007). Genetic differences may depend on ethnicity; for instance, approximately 5-10% of the Caucasian population are slow metabolizers, resulting in higher tramadol plasma concentrations and lower metabolite levels (Agenzia Italiana del Farmaco - AIFA, 2013a; Zanger et al., 2004). According to some pharmacokinetic studies, tramadol concentrations increase by 20% and its metabolite concentrations decrease by 40% in slow metabolizers (Food and Drug Administration - FDA, 2013).

Similarly, CYP2D6 inhibitors can alter this activity (Coller et al., 2012).

The O-demethylated compounds (M1, M4, M5) are further conjugated with sulfate and glucuronic acid (phase II reactions). The most abundant metabolites are M1 and its conjugates, M5 and its conjugates, and M2, with M3 and M4 and their conjugates present in smaller quantities. The metabolite M1 is pharmacologically active, exhibiting analgesic activity 2-4 times more potent than tramadol itself (Caraceni et al., 2007; Grond, Sablotzki, 2004; Lintz et al., 1981).

Approximately 20% of tramadol binds to plasma proteins (bound drug fraction) and displays high tissue affinity (Vd = 203 +/- 40 L).

Tramadol crosses the placental barrier, with minimal amounts of the drug and its active metabolite (O-demethyl derivative, M1) found in breast milk (0.1-0.02%).

Ninety percent of tramadol is excreted in the urine, either unchanged (30%) or as metabolites (60%):, 11 tramadol metabolites were identified in urine. The remaining 10% is excreted unchanged in feces (Agenzia Italiana del Farmaco - AIFA, 2014a). Discrepancies exist between humans and animals in urinary metabolite quantities: animals excrete as little as 1% due to faster drug metabolism (Lintz et al., 1981). Elimination processes, as well as O- and N-demethylation metabolic pathways, are stereoselective (differ for tramadol's two enantiomers). Consequently, due to the interaction of the two enantiomers with active metabolites, determining a pharmacokinetic profile of tramadol corresponding to its pharmacodynamic profile is challenging, and plasma concentration is not directly proportional to the site of action. The effective serum concentration usually ranges from 100-300 ng/mL (Agenzia Italiana del Farmaco - AIFA, 2014a; Grond, Sablotzki, 2004).

The half-life of tramadol (the time required to reduce drug plasma concentration by 50%) is 6 hours, regardless of the route of administration, while that of its active metabolite M1 is approximately the same (7.9 h). Elimination half-life increases in cases of hepatic or renal failure and in elderly patients (age >75 years). In such conditions, it is necessary to extend the time interval between tramadol doses (Caraceni et al., 2007). In patients with severe hepatic (cirrhosis) or renal (creatinine clearance <5 mL/min) failure, the half-life can increase up to two to three times (Agenzia Italiana del Farmaco - AIFA, 2013a).

Tramadol is also available in tablets containing paracetamol. No significant changes in pharmacokinetic parameters have been observed following the administration of the tramadol-paracetamol combination compared to the drugs administered individually. Paracetamol is absorbed more rapidly, reaching peak plasma concentration in an hour, but its half-life is shorter. Tramadol bioavailability is reduced when administered with paracetamol (Food and Drug Administration – FDA, 2013).

Classification

Chemical formula

$C_{16}H_{25}N_1O_2$

Molecular weight

263.40

Atc code

N02AX02

Bibliography

Agenzia Italiana del Farmaco – AIFA, 2013, Patrol – Summary Product Characteristics.

Agenzia Italiana del Farmaco – AIFA, 2013a, Tramadolo EG - Summary Product Characteristics.

Agenzia Italiana del Farmaco – AIFA, 2014, Prontalgin - Summary Product Characteristics.

Agenzia Italiana del Farmaco – AIFA, 2014a, Contramal - Summary Product Characteristics.

Agenzia Italiana del Farmaco – AIFA, 2015, Kolibri - Summary Product Characteristics.

Alemdar M. et al., Clin. Ther., 2007, 29 (7), 1441.

Arcioni R. et al., Anesth. Analg., 2002, 94 (6), 1553.

Aronson J., Meyler's Side Effects of Analgesics and Anti-inflammatory Drugs, 2009, Elsevier.

Bar-Or D. et al., Eur. Urol., 2012, 61 (4), 736.

Benzon H. et al., Practical Management of Pain, 2013, Elsevier Health Sciences.

Berrocoso E. et al., Psycopharmacology, 2006, 188 (1), 111.

Berrocoso E. et al., Psycopharmacology, 2007, 193 (1), 97.

Bosnjak S. et al., Srp. Arh. Celok. Lek., 2007, 135 (7-8), 453.

Browne B., Linter S., Br. J. Psichiatry, 1987, 151, 210.

Caraceni A. et al., Le complicazioni neurologiche in oncologia, 2007, Springer Science & Business Media.

Coller J.K. et al., Br. J. Clin. Pharmacol., 2012, 74 (5), 835.

Daubin C. et al., Clin. Toxicol. (Phila), 2007, 45 (8), 961.

Dayer P. et al., Drugs, 1997, 53 suppl. 2, 18.

De Backer B. et al., J. Anal. Toxicol., 2010, 34 (9), 599.

De Decker K. et al., Forensic. Sci. Int., 2008, 175 (1), 79.

De Wit D., Koomen-Botman I., Ned. Tijdschr. Geneeskd., 2013, 157 (9), A5610.

Dumo P.A., Kielbasa LA., Pharmacotherapy, 2006, 26 (11), 1654.

Dursteler C. et al., Eur. J. Pain, 2006, 10 (7), 629.

Engindeniz Z. et al., J. Headache Pain., 2005, 6 (3), 143.

Ferini-Strambi L, Marelli S., Expert. Opin. Pharmacother., 2014, 15 (8), 1127.

Food and Drug Administration – FDA, 2009, Ultram - Label Information.

Food and Drug Administration – FDA, 2010, Conzip - Label Information.

Food and Drug Administration – FDA, 2013, Ultracet - Label Information.

Food and Drug Administration – FDA, 2015, FDA drug safety communication. http://www.fda.gov/Drugs/DrugSafety/ucm462991.htm.

Food and Drug Administration – FDA, 2017, FDA drug safety communication, https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm

Fournier J.P. et al., JAMA Intern. Med., 2015, 175 (2), 186.

Freye E., Levy J., Eur. J. Pain., 2000, 4 (3), 307.

Gobel H., Stadler T., Drugs, 1997, 53 suppl. 2, 34.

Grond S., Sablotzki A., Clin. Pharmacokinet., 2004, 43 (13), 879.

Gullo A., Medicina perioperatoria Terapia intensiva Emergenza, 2003, Springer Science & Business Media.

Hagelberg N.M. et al., Eur. J. Clin. Pharmacol., 2013, 69 (4), 867.

Harati Y. et al., Neurology, 1998, 50 (6), 1842.

Harden R.N. et al., Postgrad. Med., 2013, 125 (4), 191.

Hennies H.H. et al., Arzneimittelforschung, 1988, 38 (7), 877.

Hollingshead J. et al., Cochrane Database Syst. Rev., 2006, 19 (3), CD003726.

Houlihan D.J., Ann. Pharmacother., 2004, 38 (3), 411.

Ivani G., Terapia del dolore nel bambino, 2000, SEE Editrice Firenze.

Jovanovic-Cupi V. et al., Clin. Toxicol. (Phila), 2006, 44 (2), 143.

Kaneko K. et al., Neurosci. Lett., 2014, 562, 28.

Karalliedde L. et al., Adverse Drug Interactions: A Handbook for Prescribers, 2010, CRC Press.

Kaynar M. et al., Urology, 2012, 79 (1), 145.

Kovacs G., Peter L., Neuropsychopharmacol. Hung, 2010, 12 (1), 309.

Lauerma H., Markkula J., J. Clin. Psychiatry, 1999, 60 (4), 241.

Laugesen S. et al., Clin. Pharmacol. Ther., 2005, 77 (4), 312.

Lehmann K.A. et al., Anaesthesist., 1985, 34 (1), 11.

Lehmann K.A. et al., Drugs, 1997, 53 suppl. 2:25.

Lintz W. et al., Arzneimittelforschung, 1981, 31 (11), 1932.

Loughrey M.B. et al., Forensic. Sci. Int., 2003, 134 (2-3), 232.

Lynch T., Price A., American Academy of Family Physicians, 2007, American Family Physicians, disponibile online www.aafp.org.

MacLean A.J., Schwartz T.L., Expert. Rev. Neurother., 2015, 15 (5), 469.

Marcus D., Bain P., Effective migraine treatment in pregnant and lactating women: a practical guide, 2009, Springer Science & Business Media.

Makuntus T. et al., Sci. Rep., 2019, 9 (1), 12490.

Marquardt K.A et al., Ann. Pharmacother., 2005, 39 (6), 1039.

Martyn-St. James M. et al., BMC Urology, 2015, 15, 6.

Mockenhaupt M. et al., J. Invest. Dermatol., 2008, 128 (1), 35.

Naslund S., Dahlqvist R., Lakartidningen, 2003, 100 (9), 712.

Neri E. et al., Arch. Dis. Child, 2013, 98 (9), 721.

Niscola P. et al., G. Ital. Nefrol., 2011, 28 (3), 269.

Novelli G.P. et al., Terapia del dolore, 1999, SEE Editrice Firenze.

Petzke F. et al., Support Care Cancer, 2001, 9 (1), 48.

Pittenger C. et al., Psychiatry (Edgmont), 2005, 2 (11), 34.

Planas E. et al., Eur. J. Pharmacol., 2003, 482 (1-3), 223.

Proudfoot A.T., Wright N., BMJ, 1970, 3 (5722), 557.

Rogers K.J., Thornton J.A., Br. J. Pharmacol., 1969, 36 (3), 470.

Rojas-Corrales M.O. et al., Eur. J. Pharmacol., 2005, 511 (1), 21.

Rumack B.H., Am. J. Med., 1983, 75 (5A), 104.

Saarikoski T. et al., Eur. J. Clin. Pharmacol., 2013, 69 (6), 1293.

Sadock B.J. et al., Kaplan & Sadock’s trattamento farmacologico in psichiatria: guida pratica, 2015, Edra Masson.

Salem E.A. et al., J. Sex. Med., 2008, 5 (1), 188.

Sansone R., Sansone L., Psychiatry (Edgmont), 2009, 6 (4), 17.

Scott L.J., Perry C.M., Drugs, 2000, 60 (1), 139.

Senay E.C. et al., Drug Alcohol Depend., 2003, 69 (3), 233.

Shah N.H. et al., Auton. Autacoid. Pharmacol., 2013, 33 (1-2), 1.

Silberstein S.D. et al., Headache, 2005, 45 (10), 1317.

Spiller H.A et al., J. Toxicol. Clin. Toxicol., 1997, 35 (4), 361.

Tamaskar R. et al., J. Addict. Dis., 2003, 22 (4), 5.

Tashakori A., Afshari R., Clin. Toxicol. (Phila), 2010, 48 (4), 337.

Zanger U.M. et al., Naunyn. Schmiedebergs Arch. Pharmacol., 2004, 369 (1), 23.

