TRAMADOL OVERDOSE

Introduction

Tramadol is a synthetic centrally acting analgesic agent that was introduced for its advantages over older narcotic agents including:

- Minimal sedation.
- Minimal respiratory depression.
- Reduced gastrointestinal side effects.

The main features of toxicity include:

- CNS depression.
- **Delayed** Seizures, are relatively common.
- Serotonin syndrome, in particular when taken in *combination* with another serotonergic agent.

Although tramadol is used clinically as an analgesic and has opioid effects, its toxicity profile also includes significant SNRI features. [1]

Preparation

Tablets:

Oral preparations can be immediate release or slow release.

- Immediate release: 50mg, 100mg
- Slow release (12 hour): 50mg, 100mg, 200mg, 300mg.
- Slow release (24 hour); 100mg, 200mg, 300mg.

Ampoules:

- 100mg / 2ml ampoules

Pathophysiology

Tramadol is a synthetic narcotic analgesic agent, which has the effects of:

- Weak mu-opioid partial agonist action.
- Inhibition of noradrenaline and serotonin reuptake in the CNS. Its toxic effects in overdose seem to be mainly due to this action.

Pharmacokinetics

Absorption

- Tramadol is rapidly and almost completely absorbed after oral administration
- Peak levels occur at 1-3 hours after standard preparations.
- Peak levels occur at 3-5 hours after extended release preparations.

These peak levels may be delayed however in cases of overdose.

Distribution

- Bioavailability is greater than 90%.
- Tramadol is rapidly distributed in the body, with a volume of distribution of 2 to 3 L/kg in young adults. The volume of distribution is reduced by about 25% in those aged over 75 years.
- Plasma protein binding is about 20%

Metabolism and excretion

- Tramadol is metabolized in the liver.
- Tramadol is converted to an active metabolite, by the cytochrome P450 system.

  This pathway is absent in approximately 10% of Caucasians and approximately 2% of Asians. These patients will therefore have a reduced effect with respect to the analgesia obtained from this agent.

Risk Assessment

The main potential risk is **seizures.**

These may occur when > 1.5 grams have been ingested, and their onset is usually delayed, (> 6 hours). [2]

Ingestions of more than **5 grams** of tramadol are associated with severe toxicity. [1]

Toxic doses in children are considered to be **> 10 mg/kg.** [1]

Co-ingestion of another *serotonergic* agent will increase the risk of, and severity of, **serotonin syndrome**. MAO inhibitors are a particular risk in this regard, (see also Serotonin syndrome guidelines)

Opioid effects (sedation and respiratory depression) are usually mild only, and often do not require specific treatment.

It should be noted that tramadol has limited analgesic activity, and if doses are escalated in order to get increased analgesia, toxicity is likely to develop. It is for this reason that tramadol is not recommended for use in palliative care.

Clinical Features

It is important to note that clinical effects (including seizures) may be delayed, if slow-release formulations are ingested.

Toxic effects include the following:

1. CNS:

    - Dose dependent depression of the CNS due to opioid effects, (although this is usually mild only).

2. Neurological:

    Seizures:

    - Seizures are relatively **common.**
    - Tramadol can induce seizures, *even when used within the therapeutic range.*
    - Onset of seizures can be delayed, > **6 hours**, especially in delayed preparation overdoses.
    - The risk of seizures is increased in patients with:
        - ♥ Pre-existing epilepsy
        - ♥ Other recognized risk factors for seizures, such as alcohol abuse.
        - ♥ When prescribed together with other drugs that lower seizure threshold (eg: tricyclic antidepressants, selective serotonin reuptake inhibitors, some antipsychotics and quinolones).

3. Respiratory:

    - Mild respiratory depression due to opioid effects

4. Serotonin toxicity:

- Tramadol should be used only with caution, but is probably best avoided altogether, with other serotonergic agents. There is an increased risk of the development of **serotonin toxicity** when taken in *combination* with other serotonergic agents.

5. CVS:

    - Tachycardia

    - More severe CVS effects, such as arrhythmias, or myocardial depression are uncommon, and usually only associated with massive overdose.

Investigations

None are routinely necessary, other than to determine how unwell a patient is or to rule out alternative diagnoses or secondary complications.

As with any overdose, consideration should be given to the possibility of co-ingestion, in particular:

- ECG

- Blood alcohol level and parcetamol level.

CT scan should always be considered in any patient with an altered conscious state.

Management

1. Immediate attention to ABC

    - IV access

2. Charcoal:

    - This may be considered for early presentations within 2 hours, in those who have ingested > 1.5 grams of a sustained release preparation, and are alert and cooperative; however the risk of reduced conscious state and seizures needs to be weighed against any possible benefit. [2]

    - It is safe to give in **intubated patients.**

3. Seizures:

    - These are usually self-limiting, however if prolonged or persistent should be treated with IV benzodiazepines.

4. Serotonin toxicity:

- Serotonergic symptoms such as agitation, tremor, myoclonic jerks, and tachycardia can be treated with titrated IV benzodiazepines.

  This treatment will also be useful for the *prevention* of seizures.

For more severe serotonergic toxicity see separate document on Serotonin Toxicity.

5. Naloxone:

   - This can be used to treat respiratory depression and/ or CNS depression, but will not reverse any other toxic effects.

Disposition

Adults who have ingested > **1.5 grams** (standard preparation) must be observed for a *minimum* of **12 hours** and until symptom free. They should have IV access in anticipation of seizures.

Children who have ingested > **10mg/kg** should be observed for 12 hours and until symptom free.

Overdose with **slow release** preparations will require longer observation periods (16-24 hours) [1]

References:

1. eTG- November 2015.

   - Tramadol Overdose in Toxicology & Wilderness Therapeutic Guidelines 2nd ed 2012.

2. Tramadol in: L Murray et al. Toxicology Handbook 3rd ed 2015.

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