CASE REPORT

An uncommon presentation of a common drug overdose – the dangers of underestimating Tramadol

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ABSTRACT

Tramadol hydrochloride {(1RS, 2RS)-2-[dimethylamino] methyl]-1-(-3-methoxyphenyl) - cyclohexanol hydrocholoride)} is a commonly prescribed analgesic that is licensed in the UK for moderate to severe pain. Its analgesic action is mainly as a result of its serotonin and noradrenalin reuptake inhibitor (SNRI) like activity 2. However, the more commonly promoted mode of action is as a μ-receptor opioid agonist, for which it has only a weak affinity.

Despite its mode of action, specific features of SNRI toxicity have not previously been reported with tramadol overdose. Furthermore, within the tramadol Summary of Product Characteristics and several toxicology databases the treatment of tramadol overdose focuses on reversing opioid toxicity alone. We present a case of tramadol overdose complicated by combined features of opioid toxicity and SNRI toxicity.

Tramadol hydrochloride {(1RS, 2RS)-2-[dimethylamino] methyl]-1-(-3-methoxyphenyl)-cyclohexanol hydrocholoride)} is a commonly prescribed analgesic that is licensed in the UK for moderate to severe pain [1]. Its analgesic action is mainly as a result of its serotonin and noradrenalin reuptake inhibitor (SNRI) like activity 2. However, the more commonly promoted mode of action is as a μ-receptor opioid agonist, for which it has only a weak affinity [2].

Despite its mode of action, specific features of SNRI toxicity have not previously been reported with tramadol overdose. Furthermore, within the tramadol Summary of Product Characteristics and several toxicology databases the treatment of tramadol overdose focuses on reversing opioid toxicity alone. We present a case of tramadol overdose complicated by combined features of opioid toxicity and SNRI toxicity.

The case

A 43 year old lady presented having taken a significant tramadol overdose 6 hours prior to admission. She admitted to taking between 3 and 4 grams (ffi50mg / Kg) of the drug. She denied recently taking any other medication or alcohol. Between the time of overdose and her presentation in the emergency department she had a tonic clonic seizure lasting several minutes. On admission, she was drowsy with a Glasgow Coma Score of 14/15 (E3V5M6). Physical examination revealed a tachycardia of 110 bpm with a blood pressure of 110/80 mmHg. Her pupils were mid point, and her temperature was 36.80C. Her ECG and QT interval were normal (figure 1).

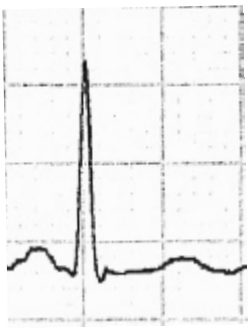

Figure 1: Time 12:17; QTc 438ms

Over the next hour she developed signs of opioid toxicity with miosis, and a respiratory rate of less than 8 breaths per minute. Her oxygen saturation on 2 litres of oxygen dropped to 86%. However, arterial blood gas measurement showed a mixed respiratory and metabolic acidosis, with a pH 7.12 (7.36–7.44), PO2 of 10.5 kPa (11.3–12.6), PCO2 7.4 kPa (4.7–6.0), HCO32- 8 mmol/L (19–24), base excess minus 14 mmol/L (±2), and a lactate of 7.4 mmol/L (<2.0). Paracetamol, salicylates, and alcohol were not detected. Potassium levels were normal at 4.0 mmol/L (3.6 – 5.0), with a magnesium at the lower end of the reference range at 0.82 mmol/L (0.70 – 0.90). Her urine toxicology showed no other drug having been taken. Her ECG had changed to show a prolongation of her corrected QT interval (figure 2).

She had a further brief tonic clonic seizure soon afterwards, treated with an intravenous bolus of benzodiazepine. Her GCS had dropped to 10/15 (E2V3M5). In view of her respiratory and CNS depression she was given two boluses of

naloxone, to which she briefly responded. However, her corrected QT interval continued to rise (figure 3), and her acidosis continued to worsen. She was treated with intravenous fluids and an intravenous naloxone infusion. Over the next few hours her acidosis resolved and her respiratory rate normalised. Her corrected QT interval also normalised (figure 4). She was discharged home 2 days later.

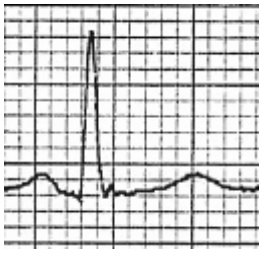

Figure 2: Time 17:10; QTc 454ms

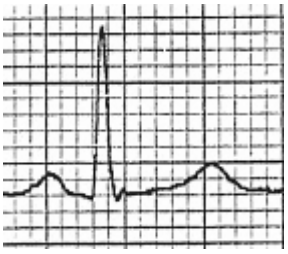

Figure 3: Time 20:45; QTc 461 ms

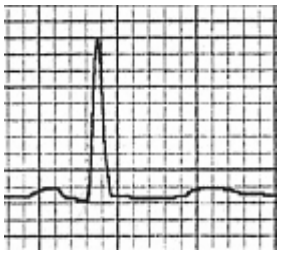

Figure 4: Time 08:01; QTc 435 ms

Discussion

Tramadol is a commonly used opioid used for moderate to severe pain management. When taken in overdose it is known to be associated with significant morbidity and mortality [3]. Between 1995 and 2002 1714 cases of tramadol overdose were reported to the Drug Abuse Warning Network [4]. The most common features of overdose are those associated with its opioid activity – these most frequently include central nervous system depression, nausea and vomiting, tachycardia, and seizures [3]. Theoretically, tramadol overdose should also present with features of the serotonin syndrome due to the SNRI properties [5]. These features should include neuromuscular hyperactivity (myoclonus and hyperreflexia), autonomic hyperactivity (tachycardia, pyrexia) and altered mental state (usually agitation, excitement and later confusion). Higher doses can be associated with cardiovascular collapse, coma, and respiratory depression. Each of these features should be treated accordingly, with no other specific treatment for SNRI toxicity.

Whilst the current report is limited buy the lack of an available plasma tramadol concentration, the presence of no other drug in her urine toxicology screen; the history from the patient, corroborated by her partner; as well as several recently dispensed empty tramadol blister packs, we feel she had taken a very significant overdose. Our patient had features consistent with opioid overdose – the respiratory depression with miosis and the respiratory acidosis. She also exhibited features of SNRI toxicity – seizures, prolongation of her QT interval and the metabolic acidosis. It was felt the seizures were unlikely to have contributed to the metabolic component of her mixed acidosis because they were relatively short, and the blood gases were done at least an hour after they had stopped. In addition, her Naranjo probability score was 6 [6].

The O-desmethyl metabolite (M1) of tramadol, produced by cytochrome p450 shows a higher affinity to μ-receptors than the parent compound. The half life of the M1 metabolite is 9 hours, compared to only 2 hours for tramadol. Both compounds have monoaminergic activity, demonstrating inhibition of noradrenaline and serotonin reuptake, thereby blocking nociceptive impulses at the spinal level [7].

The UK Summary of Product Characteristics only mentions the SNRI action in passing, and only the opioid effects when taken in overdose [8]. Toxicology databases also state that the mainstay of treatment should still be naloxone to antagonise the opioid effects of tramadol [4].

In summary we have presented a case of a drug commonly taken in overdose that is associated with significant morbidity and mortality. Clinicians should be aware that tramadol has SNRI properties that can confuse the clinical picture and patients may present with symptoms and signs out of keeping with uncomplicated opioid overdose. Toxicology databases and the UK Summary of Product Characteristics should be updated to incorporate this information.

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