

# Is There A Ceiling Effect For Patient Controlled Analgesia Using Tramadol? A Case Report And Review Of The Literature.

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## Abstract

Patient controlled analgesia (PCA) devices are a commonly used method of self-administered intravenous opioid titration post-surgery. Tramadol PCA has been shown to be a safe and effective modality of post-operative analgesia when compared with morphine. Reports of Tramadol toxicity are well documented in the literature; however there are no clear guidelines on maximal doses that should be administered by PCA. We report a case of seizure related to Tramadol and review the literature to determine a safe dosing range for Tramadol PCA.

## INTRODUCTION

Opioid analgesics are an important component of a multimodal analgesic approach to post-operative surgical pain. Tramadol has particular advantages over morphine and other opioids, making it an attractive alternative for use in PCA. More serious side effects of traditional opioids, including respiratory depression, sedation, tolerance, addiction potential, constipation or ileus are less likely with Tramadol [1-2].

Recommended therapeutic doses of Tramadol are 400mg orally or 600mg parenterally per 24 hours. The current dosing limits may reflect past views that tramadol acted as a partial agonist with a ceiling effect [3]. Tramadol PCA has been used at our institution for nearly a decade. Dosages as high as 2000mg have been administered in a 24-hour period without serious adverse incidents being reported. Most commonly reported side effects have included nausea and vomiting, sedation, confusion, sweating, tachycardia and suboptimal analgesia. We have had no previous reports of seizures.

## CASE REPORT

A 46-year-old healthy female was admitted to hospital for elective left ankle fusion. There was no history of epilepsy and she did not take any regular medications. Her husband described a history strongly suggestive of Obstructive Sleep Apnea (OSA). A spinal anaesthetic was performed without intrathecal opiate and the patient taken to the post-

anaesthetic care unit (PACU) post-procedure. No additional intravenous opioids were administered in PACU. Tramadol PCA with 20mg bolus and 5 minute lockout was commenced as a component of multimodal analgesia for post-operative pain control.

The Acute Pain Service (APS) was asked to review the patient's analgesia later that evening due to unsatisfactory pain scores. 300mg of IV (Intravenous) Tramadol had been administered in 5 hours postoperatively. A Ketamine infusion was commenced at 4mg/hr to supplement the Tramadol PCA. The following morning the patient reported her pain score as 3/10. On a scale of one to ten, a score of zero equates to no pain and ten equals the worst pain the patient has ever experienced. 920mg Tramadol had been administered in 16 hours. The Ketamine infusion was ceased and PCA continued.

Later that morning patient had a witnessed, self-limited tonic clonic seizure of approximately 20 seconds duration while lying in bed. The Tramadol PCA was discontinued and Fentanyl PCA commenced once the patient was no longer postictal. Clinical neurological and other routine investigations were within normal limits. No further seizures occurred and the patient was discharged from hospital three days later.

## DISCUSSION

There have been several case reports of tramadol

precipitating seizures in non-epileptic patients at or above the recommended doses [4]. Poisonings involving Tramadol have reported ingestions ranging from 100 – 14000mg with an average of 1650mg in one series of patients. Doses of tramadol in non-survived cases ranged between 5000mg and 8200mg. Fatalities from tramadol overdosing are rare and are related to pharmacological extensions of its therapeutic effects. Symptoms typically include gastrointestinal, CNS, and cardiovascular abnormalities [5]. The risk of fatality increases when tramadol is co-ingested in excess with other drugs, including central nervous system depressants, other analgesics, muscle relaxants and anti-depressants [6].

Tramadol provides post-operative pain relief comparable to pethidine; however, efficacy of analgesia is subject to genetic polymorphisms. 8-10% of the Caucasian population are genetically poor metabolizers of CYP2D6 substrates and experience reduced analgesia from tramadol. 3-5% are ultra-rapid metabolizers. Gene duplication results in enhanced metabolism and analgesic efficacy, and can contribute to toxicity in patients with renal or hepatic impairment [7-9].

At our institution Tramadol PCA is most commonly prescribed for orthopaedic procedures, usually ORIFs in long bones or joint replacements, in patients who had either a history of obstructive sleep apnea or are obese. The next most common indications are for neuropathic pain or a history of opioid tolerance. Tramadol PCA is not routinely prescribed for patients who are on regular anti-depressants, psychotropic medication, have a history of epilepsy, or have had hypersensitivity reactions or previous nausea and vomiting with tramadol in the past.

A retrospective Acute Pain Service (APS) audit from May 2009 to April 2010 including 119 patients across five surgical services where Tramadol PCA was prescribed post-operatively demonstrated a mean daily dose of 619 mg to treat acute pain. Average maximum dose at 48 hours, which represents the average duration of PCA usage, was 2290mg (unpublished data). The highest cumulative dose was 1480mg in 24 hours and 4680mg in 48 hours in a 66 year old morbidly obese male (BMI 41) with history of Type 2 Diabetes Mellitus and OSA who underwent a total knee replacement. No significant adverse effects were reported.

Literature reports of frequent nausea, vomiting, and drowsiness are often cited as the reason for poor patient satisfaction scores with Tramadol PCA. However there is disagreement as to whether Tramadol causes more nausea

and vomiting compared to Morphine [10-11]. Our institution recorded higher Tramadol doses than previously cited within the literature. Possible explanations for some of our results may reflect the use of 5HT<sub>3</sub> antagonists as first-line antiemetic agents. Ondansetron has been shown to reduce the analgesic efficacy of Tramadol; however, it was noted that some patients using large doses of tramadol were not administered 5HT<sub>3</sub> antiemetics [12]. A large proportion of Tramadol PCAs were in patients with OSA undergoing painful orthopaedic procedures where Tramadol may lack analgesic efficacy compared to Morphine [13]. Differing anaesthetic techniques, varying intraoperative loading regimens, existing chronic or neuropathic pain issues, and impact of pharmacogenetics may also explain some of the varying responses to Tramadol post operatively.

## **CONCLUSION**

Tramadol PCA can be considered an appropriate choice where patient, clinical or surgical factors place the patient at an increased risk of post-operative respiratory complications. Defining an ideal patient population for post-operative Tramadol PCA is difficult due to the nature of the surgery, anticipated analgesic requirements, comorbidities, current medications and intrinsic pharmacogenetic polymorphisms. Administration of greater than 1000mg Tramadol in a 24-hour period by PCA should prompt the clinician to consider changing to another opioid.

The addition of a small-dose Ketamine infusion to tramadol has been shown to improve analgesia after major abdominal surgery [14]. Little has been reported on the influence of Ketamine in patients experiencing Tramadol-induced seizures, and there is conflicting data as to whether Ketamine is a pro-convulsant [15]. With no history of epilepsy and a small dose infused, it is unlikely Ketamine was a contributing factors to this patient's seizure.

## **AUTHOR'S CONTRIBUTIONS**

AL was the Anaesthetic Registrar who reviewed the patients post operative analgesia and performed the literature review. Both authors were involved in the writing of the report. Both authors read and approved the final manuscript.

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