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# **Tramadol-induced Adrenal Insufficiency**

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Dear Editor,

We present a case of a patient suffering from non-specific abdominal pain on long term tramadol, a  $\mu$ -opioid receptor agonist, who presented with adrenal insufficiency. This case raises awareness of the potential of opioids to influence adrenal status and is important as the effects of long term opioid use on the hypothalamo-pituitary-adrenal axis (HPA) is still conflicting. The majority of studies have mainly investigated acute effects, whereas chronic effects may differ considerably [1].

## Case Report

A 21 year old female was referred to Endocrinology Outpatients with a three year history of non-specific abdominal pain, lethargy, dizziness, vomiting and headaches. She had been investigated thoroughly having also had a gastrocolonoscopy, a barium small bowel meal and a computed tomography of the abdomen; all of which were normal. One month prior to her referral, she was admitted to hospital with a three day history of dizziness, blurred vision, vomiting and pressure-like headaches. She was found to have an abnormal prolactin of 1968mU/l (normal range 59 - 619mU/l) and an incidental finding of a pituitary microadenoma on MRI. A Synacthen test was mildly abnormal with a baseline 0900h cortisol of 54nmol/l (at 0900h: 198 - 720nmol/l) and a 30-minute cortisol of 537nmol/l (normal Synacthen test: 30-minute cortisol >550nmol/l). Her medications included Tramadol 50mg TDS, Sumatriptan 50mg OD, Metoclopramide 10mg TDS, Omeprazole 40mg OD and Ibuprofen 400mg TDS.

She was advised to stop Metoclopramide and Tramadol. Her prolactin levels improved to 216mU/l and a repeat Synacthen test normalised. Other endocrinological tests were as follows: TSH 1.94mU/l (0.35 – 4.5mU/l), free T4 14.3pmol/l (10.0 – 19.8pmol/l), free T3 4.1pmol/l (3.5 – 6.5pmol/l), IGF1 192mcg/l (115 – 340mcg/l), FSH 4.7IU/l (2.5 – 10.2IU/l), LH 10.9IU/l (1.9 - 12.5IU/l), Oestradiol 297pmol/l (40 – 606pmol/l), Testosterone 2.3nmol/l (0.5 – 2.6nmol/l). A diagnosis of tramadol-induced adrenal insufficiency was considered whilst metoclopramide in addition to stress from the acute admission, highly likely caused the hyperprolactinaemia.

Two months later, she was readmitted with similar symptoms. Her medications included Tramadol 100mg QDS which was inadvertently restarted by her GP for persistent abdominal pain. She was also having Sumatriptan 50mg OD, Cyclizine 50mg TDS, Omeprazole 40mg OD and Ibuprofen 400mg tds. A repeat MRI head showed no changes to the size of the pituitary microadenoma. A Synacthen test revealed adrenal insufficiency but the rest of the pituitary profile, including prolactin, was normal. Cortisol levels from the Synacthen test at 0900h were 45, 307 and 419nmol/l at 0, 30 and 60 minutes respectively and a 0900h adrenocorticotrophic hormone (ACTH) was relatively low at 9.7ng/l (9am <46ng/l; at midnight <15ng/l). She improved significantly initially with intravenous then oral low dose hydrocortisone. A diagnosis of tramadol-induced adrenal insufficiency was made. Hence, tramadol was stopped and hydrocortisone was rapidly tailed down. Repeat Synacthen tests and ACTH off tramadol normalised (Figure 1).

Our case report shows that stopping long term tramadol improved the function of the HPA axis in a patient diagnosed with secondary adrenal insufficiency resulting in a superior quality of life. The sequence of events as carefully highlighted in figure 1 and recurrence of adrenal insufficiency on drug rechallenge support tramadol as being the cause for this event. Further, metoclopramide, a dopamine D<sub>2</sub> receptor antagonist with mixed 5-HT<sub>3</sub> receptor antagonist/5-HT<sub>4</sub> receptor agonist activity [2] and known to cause hyperprolactinaemia [3], is not known to cause adrenal insufficiency. Our patient was not on metoclopramide when readmitted to hospital and re-diagnosed with adrenal insufficiency, making tramadol the most likely cause for this adverse effect. She was also not taking any over the counter drugs during both admissions.

A few non-systematic studies have investigated the effects of opioids on the HPA axis but results have been conflicting. In humans acute administration of 30mg of SR morphine resulted in a decreased cortisol, ACTH and  $\beta$ -endorphin response to corticotropin-releasing hormone (CRH) when compared to placebo whilst the response was higher after naloxone. This indicated that ACTH release is physiologically inhibited by endogenous opioids at the pituitary level [4]. Further, heroin addicts have been shown

to have a loss of the circadian rhythms of proopiomelanocortin peptides [5]. Suppression of the HPA axis was shown in patients on long term intrathecal morphine [6] and has also been reported in three patients on chronic transdermal fentanyl, hydromorphone and methadone respectively [7-9]. In contrast 22 patients on an oral mean morphine dose of 78mg/day for around 31 months showed no significant difference in the 30 minute cortisol post-Synacthen when compared to the 13 patients in the non-opioid analgesia group [10].

One of the main reasons for this inconsistency in studies could be the variable response to opioids by different individuals. A potential explanation for this could be the presence of  $\mu$ -opioid receptor polymorphisms, such as the A118G polymorphism, which may predict the cortisol response to naloxone and has been shown to increase  $\beta$ -endorphin binding affinity, placing greater inhibitory tone on hypothalamic CRH neurons [11]. Tramadol, a synthetic piperidine analog of the phenantherane alkaloid codeine, is a  $\mu$ -receptor agonist [12]; hence possibly explaining why this patient, who potentially could harbour this polymorphism developed dose-related adrenal insufficiency. Three classes of opioid receptors have been identified, namely mu( $\mu$ ), delta( $\Delta$ ) and kappa( $\kappa$ ) [13, 14] and different polymorphisms at these different receptors may determine one's distinct HPA axis response to opioids.

To our knowledge this is the first clinical case of tramadol-induced adrenal insufficiency. This drug resulted in the suppression of the HPA axis hence making the patient unable to respond to stressful events with an increased risk of mortality and a poor quality of life. As there is no robust evidence suggesting that opioids definitely cause adrenal insufficiency, there are currently no guidelines for the routine investigation of the HPA axis in patients on chronic opioids. Hence, symptoms of adrenal insufficiency in patients on long term opioids should instigate physicians to assess adrenal status. Predicting which opioid formulations, and at what dose, are more likely to cause adrenal insufficiency in a particular patient is not possible at present. Systematic studies, including genetic studies, to assess the effects of opioids on the HPA axis are necessary.

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## Legends

**Figure 1 :** Graph indicating results of 250mcg Short Synacthen Test (baseline and 30-minute cortisol) at differences phases of Tramadol treatment. Synacthen test is normal if 30-min cortisol > 550nmol/l (- - -).

Figure 1

# Synacthen Tests vs Tramadol Dose

