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LETTER TO THE EDITORS

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 μ-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) are still unresolved. 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 3-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 3-day history of dizziness, blurred vision, vomiting and pressure-like headaches. She was found to have an abnormal prolactin of 1,968 mU/l (normal range 59–619 mU/l) and an incidental finding of a pituitary microadenoma on MRI. A synacthen test was mildly abnormal with a baseline 0900 h cortisol of 54 nmol/l (at 0900 h: 198–720 nmol/l) and a 30-min cortisol of 537 nmol/l (normal synacthen test: 30-min cortisol >550 nmol/l). Her medications included tramadol 50 mg TDS, sumatriptan 50 mg OD, metoclopramide 10 mg TDS, omeprazole 40 mg OD and ibuprofen 400 mg TDS.

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

Two months later, she was readmitted with similar symptoms. Her medications included tramadol 100 mg QDS, which had inadvertently been restarted by her GP for persistent abdominal pain. She was also taking sumatriptan 50 mg OD, cyclizine 50 mg TDS, omeprazole 40 mg OD and ibuprofen 400 mg TDS. A repeat MRI of the 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 0900 h were 45, 307 and 419 nmol/l at 0, 30 and 60 min respectively, and a 0900 h adrenocorticotropic hormone (ACTH) was relatively low at 9.7 ng/l (0900 h <46 ng/l; at midnight <15 ng/l). She improved significantly initially

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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 (Fig. 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 Fig. 1 and recurrence of adrenal insufficiency on drug rechallenge support tramadol as being the cause for this event. Further, metoclopramide, a dopamine D_2 receptor antagonist with mixed 5-HT3 receptor antagonist/5-HT4 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 30 mg of SR morphine resulted in a decreased cortisol, ACTH and β-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 propiocortin peptides [5]. Suppression of the HPA axis has been shown

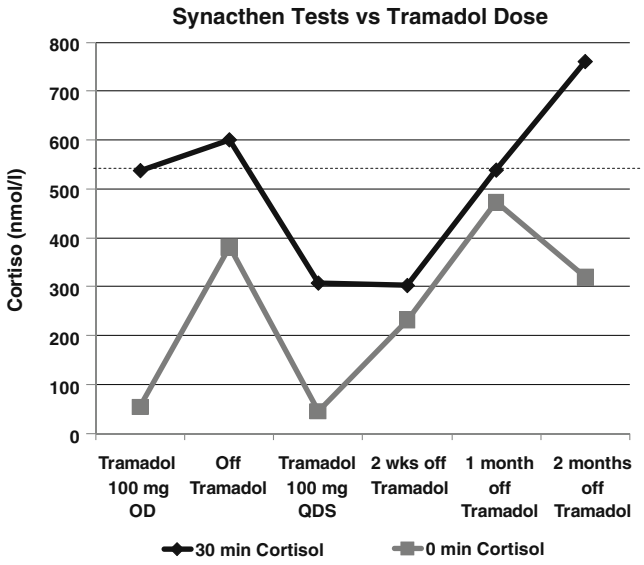

Fig. 1 Graph indicating results of 250 μg short synacthen test (baseline and 30-min cortisol) at different phases of tramadol treatment. Synacthen test is normal if 30-min cortisol>550 nmol/l (*dotted line*)

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 78 mg/day for around 31 months showed no significant difference in the 30-min 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 μ-opioid receptor polymorphisms, such as the A118G polymorphism, which may predict the cortisol response to naloxone and which has been shown to increase β-endorphin binding affinity, placing greater inhibitory tone on hypothalamic CRH neurons [11]. Tramadol, a synthetic piperidine analog of the phenanthrene alkaloid codeine, is a μ-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 (μ), delta (Δ) and kappa (κ) [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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