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Low-dose hydrocortisone replacement improves wellbeing and pain tolerance in chronic pain patients with opioid-induced hypocortisolemic responses. A pilot randomized, placebo-controlled trial

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Abstract Long-term opioid therapy has been associated with low cortisol levels due to central suppression of the hypothalamic—pituitary—adrenal axis. The implications of hypocortisolism on wellbeing have not been established. Our aim was to determine whether intervention with physiologic glucocorticoid replacement therapy improves wellbeing and analgesic responses in patients with chronic non-cancer pain on long-term opioid therapy with mild cortisol deficiency. We performed a pilot randomized, double-blind, placebo-controlled crossover study of oral hydrocortisone replacement therapy in 17 patients recruited from a Pain Clinic at a single tertiary center in Adelaide, Australia. Patients were receiving long-term opioid therapy (≥20 mg morphine equivalents per day for ≥4 weeks) for chronic non-cancer pain with mild hypocortisolism, as defined by a plasma cortisol response ≤350 nmol/L at 60 min following a cold pressor test. The crossover intervention included 28-day treatment with either 10 mg/m^2/day of oral

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hydrocortisone in three divided doses or placebo. Improvement in wellbeing was assessed using Version 2 of the Short Form-36 (SF-36v2), Brief Pain Inventory-Short Form, and Addison's disease quality of life questionnaires; improvement in analgesic response was assessed using cold pressor threshold and tolerance times. Following treatment with hydrocortisone, the bodily pain ($P = 0.042$) and vitality ($P = 0.013$) subscales of the SF-36v2 were significantly better than scores following treatment with placebo. There was also an improvement in pain interference on general activity ($P = 0.035$), mood ($P = 0.03$) and work ($P = 0.04$) following hydrocortisone compared with placebo. This is the first randomized, double-blind placebo-controlled trial of glucocorticoid replacement in opioid users with chronic non-cancer pain and mild hypocortisolism. Our data suggest that physiologic hydrocortisone replacement produces improvements in vitality and pain experiences in this cohort compared with placebo.
Trial registration: Therapeutic Goods Administration Clinical Trials Notification Scheme (Drugs), Trial Number 2012/0476.

1. Introduction

Chronic pain is experienced by 20% of the population (Reid et al., 2011). The long-term use of opioid analgesia is becoming increasingly common, particularly in sufferers of chronic non-cancer pain (CNCP) (Manchikanti et al., 2012). This increase in opioid consumption is accompanied by considerable risks; common side effects include constipation, nausea, sedation and physical dependence, while more serious complications include hyperalgesia, immunosuppression, respiratory depression, overdosage death, and neuroendocrine dysfunction (Benyamin et al., 2008; Baldini et al., 2012). Chronic pain and opioid use are also associated with a high incidence of anxiety and depression as well as lower quality of life and inferior self-rated health (Becker et al., 1997; Eriksen et al., 2003).

Secretion of the glucocorticoid cortisol is tightly regulated to maintain homeostasis (Chrousos, 2009). Hypothalamic secretion of corticotropin releasing hormone (CRH) is a major driver of pituitary adrenocorticotropic hormone (ACTH) production, which then stimulates secretion of cortisol from the adrenal cortex. Opioids have central effects on the hypothalamic–pituitary–adrenal (HPA) axis, acting via low-affinity delta (δ) and kappa (κ) opioid receptors, where binding results in tonic inhibition of the excitatory α_1-noradrenergic pathways that stimulate the release of CRH (Grossman and Besser, 1982; Grossman et al., 1986; Torpy et al., 1993). This is confirmed by the increase in plasma ACTH and cortisol seen following blockade of these opioidergic pathways by the opioid receptor antagonist naloxone (Volavka et al., 1979; Torpy et al., 1993). Direct inhibitory effects of opioids on steroidogenesis by the gonads and adrenals are also described (Aloisi et al., 2009). Episodes of acute adrenal insufficiency in patients receiving chronic opiates have been reported, with recovery of the HPA axis when opioid doses are reduced (Abs et al., 2000; Oltmanns et al., 2005; Mussig et al., 2007). Detailed information and clinical awareness related to opioid-induced hypocortisolism is limited (Vuong et al., 2010) despite the knowledge that states of cortisol deficiency are associated with fatigue, hypotension, altered mood and neurocognitive function, working disability and impaired quality of life (Lovas et al., 2002; Hahner et al., 2007). These signs and symptoms may overlap with symptoms experienced with chronic pain (Eriksen et al., 2003).

Activation of the HPA axis, as well as the adrenomedullary hormonal system and sympathoadrenergic systems, occur in a stressor-specific manner (See Goldstein and Kopin, 2007 for review). Stressors including hemorrhage, insulin, cold, pain and immobilization produce individualized neuroendocrine responses (Pacak et al., 1998). With specific regard to the HPA axis, different peak cortisol responses have been found to the insulin tolerance test, the low-dose (1 μg) Synacthen test and the high-dose (250 μg) Synacthen test, suggesting that individualized cut-off values should apply to each stimulus (Cho et al., 2014). In this study we have utilized the cold pressor test (CPT), a moderate physiologic stimulator of the HPA axis (Al'absi et al., 2002; Smeets et al., 2008). The CPT is a widely used experimental method for inducing systemic stress via pain (Mitchell et al., 2004) and allows simultaneous study of the HPA axis integrity and pain parameters. We have found that the plasma cortisol response to CPT is impaired in patients receiving long-term opioid therapy (LTOT) (Haylock, 2012) and using our methodology, have obtained method-specific reference ranges to detect hypocortisolemia in these patients.

Although low cortisol levels in patients using chronic opioids have been described (Palm et al., 1997; Abs et al., 2000; Oltmanns et al., 2005; Mussig et al., 2007), the implications for health and wellbeing and the response to hormone replacement have not been established. To date, no study has investigated the pain and health-related quality of life effects of glucocorticoid replacement in chronic opioid users. Therefore, we undertook a pilot placebo-controlled double-blind crossover study to determine whether intervention with physiologic glucocorticoid replacement therapy can improve wellbeing and analgesic responses in subjects on LTOT with mild cortisol deficiency.

2. Patients and methods

2.1. Study 1

We undertook a preliminary cross-sectional observational study to determine whether the CPT could detect mild