Opiates and the adrenal: the tip of the iceberg?

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Morphine-like compounds based on opium and derived from the opium poppy, *Papaver somniferum*, have been known for millennia, and their use recurs throughout the ages in personal reports and in world literature. For many decades their use was, if not fully condoned by society, tolerated as an effective means of ameliorating pain and indeed for 'recreational' purposes. The Opium Wars in the nineteenth century pitched the enthusiastic British traders in China against the local authorities who wished to control their use, with the eventual triumph of commercial capitalism and British firepower. In late nineteenth century London such opium dens were an accepted part of the Limehouse landscape, at least according to Charles Dickens, and frequented by well-connected gentlemen; indeed Coleridge's epic poem *Kubla Khan* was said to be written under the influence of opium, while Thomas de Quincey immortalised the habit in his *Confessions of an English Opium-Eater*.

However, over time and especially in the twentieth century, such opium-like compounds, the opiates, increasingly became drugs of abuse in addition to their profound analgesic effects, with heroin in particular becoming a global scourge. In addition, various analogues of the opiates were synthesised, with varying potencies, hoping to emphasise the analgesic efficacy while limiting their addictive potential. Unfortunately, it has been difficult to separate these two factors, and with the active encouragement of pharmaceutical companies, drugs such as oxycodone have become a major source of addiction and distress. Thus, in addition to their widespread use as highly effective analgesic agents in medicine, opiates have moved from an illegal phenomenon as part of the global drug trade to a phenomenal prescription-agent problem in many parts of the developed world. It has been estimated that since 1999, 200 000 Americans have died

from oxycodone and allied prescription opiates, while in recent years US clinicians have issued a quarter of a billion opiate prescriptions annually (1). The pharmacology of opiates has become literally of deadly interest. Thus, their pharmacology, and especially their effects on neuroendocrine axes, is of very considerable interest.

In 1973 Hughes and Kosterlitz described the endogenous opiate-like compound, met-enkephalin, as the first opioid (2). Subsequently, other opioids were described, the endorphins and dynorphins, and in due course their specific receptors were identified, principally δ , μ and K (and possibly σ), with putative ligands of enkephalin, endorphin and dynorphin for the first three respectively. Animal studies revealed the presence of each of these opioid classes within the hypothalamo–pituitary axis, while experimental studies in humans demonstrated the effect of their exogenous administration. Many of these effects were similar to those seen after administration of opiates such as morphine. In terms of the neuroendocrine axes, in our studies as well as others, opioid analogues were able to potently suppress the release of the gonadotrophins FSH and LH (3) and of ACTH and cortisol (4); most studies suggested there were actions at the level of the hypothalamus, with suppression of gonadotrophin-releasing hormone and the ACTH secretagogue CRH-41 and probably vasopressin (5).

As the different types of opioid receptor was shown to have different sensitivities to antagonism with the opiate antagonist naloxone, varying doses of naloxone were administered to humans in different pathophysiological situations to reveal the nature and type of endogenous opioid 'tone'. Summarising very many of these studies, it was established that the hypothalamo–pituitary–adrenal (HPA) axis is subject to a continuous relatively invariant tone over 24 h requiring high doses of naloxone to reveal

it (6, 7), while the gonadotrophins showed sensitivity to low doses of naloxone, with a tone which varied over the menstrual cycle (8), and which was dramatically increased in hyperprolactinaemia (9, 10). The amenorrhoea of hyperprolactinaemia may thus at least in part be opioid mediated. These potent effects of endogenous and exogenous opiates and opioids were not subsequently extended to any major extent, although it was realised that there was profound suppression of the pituitary–gonadal axis in those addicted to potent opiates such as methadone and heroin (11). Indeed, the effects of opium on sexual function had also been recorded down the ages, with a detailed description being given by the Persian physician Avicenna (Abu Ali al-Husayn ibn Sina), who was born near present-day Bukhara in Uzbekistan. However, when one turns to the pituitary and adrenal, rather surprisingly, effects on the HPA axis have been little studied, a serious omission in view of the considerable increase in prescription-opiate use and abuse, as noted above.

In the recent study by Lamprecht *et al.* (12), groups from Brisbane and Adelaide in Australia have attempted to explore whether and how relevant are the effects of opiates on hypothalamo–pituitary axes, particularly the HPA and gonadal axes. They recruited a group of 40 patients from a Chronic Pain Clinic and used a parallel control group of 25 subjects in order to assess the effects of opiate use on basal pituitary hormone status, as well as their responses to dynamic stimulation of the HPA axis. The patients were mainly on oxycodone, and they used a dose formula based on morphine equivalents whereby oxycodone is considered 1.5 times more potent than morphine. The two groups were then subject to baseline hormonal assessment as well as a short *Synacthen* test (ACTH(1–24) 250 µg) or a metyrapone test or both. The mean morphine equivalent dose in the patient group was 74 mg. The groups were then compared in terms of their basal and stimulated hormone levels, as well as their responses to a variety of questionnaires.

Assuming a basal cortisol of <138 nmol/L was 'subnormal', they reported that 20% of their patients had subnormal levels compared to none of the controls. Overall, 22.5% of patients were considered to have failed the basal or simulated tests of cortisol reserve. This was rather higher than a previous uncontrolled study from Edinburgh (13). However, in the present study none failed if their morphine equivalent dose was <60 mg a day, while this was frequently seen in those on 100 mg or greater. There was no significant evidence of hypogonadism in either sex, any minor differences being probably

accountable to changes in BMI, while the questionnaire analysis did not reveal any major unexpected findings.

One possible criticism of the study would be of the tests and criteria used to substantiate hypocortisolism. They used a serum cortisol of 250 nmol/L as their threshold for assuming a normal HPA axis, justified from several rather older studies, although others have suggested much higher values of the order of 350 nmol/L using most modern assays (14), and even higher with some assays. It is not often realised how assay dependent is the measurement of cortisol (15), so much care needs to be taken in extrapolating to other centres and laboratories without a clear description of the assay in use. Furthermore, most would use a significantly lower 30-min cut-off for a normal *Synacthen* test than the 60-min value they have used (15), although they reported normative results from their own centre. They are also one of the few centres utilising the metyrapone test as a measure of cortisol reserve. Nevertheless, taking the results as presented, there is little doubt that a substantial percentage of patients on opiates show a disturbed HPA axis, an important positive finding. But is this clinically significant, and if not, why not?

It is surprising that such studies have not been more in evidence in the endocrine literature, as quite clearly profound suppression of the HPA axis may have important clinical consequences. It would appear from this study that low doses of exogenous opiates are relatively sparing of the HPA and pituitary–gonadal axes and are thus unlikely to have any major sequelae. The lack of effect on the pituitary–gonadal axis, as reported here, is especially surprising and probably reassuring in terms of any requirement for endocrine replacement therapy. Previously, chronic opiate use has been strongly associated with gonadotrophin suppression (16), and indeed, many case reports such as our own have shown very profound inhibition of both pituitary–gonadal as well as pituitary–adrenal blockade after short-term use (17). It may be that these effects are highly dose and time dependent. However, the marked suppression of the HPA axis reported here, admittedly in a minority of patients and those on the highest doses, does raise significant questions as to the clinical significance of these findings. Most importantly, are these subnormal basal and particularly stimulated levels of cortisol associated with increased morbidity and possibly mortality? It is generally assumed that a subnormal response to ACTH(1–24) requires consideration of glucocorticoid replacement, at least during infective illness, trauma or surgery, but does this apply to this patient group? Are we unaware of significant morbidity in

patients on high doses of opiates or is this a non-problem? For example, patients on potent opiates for pain relief, especially when prescribed for malignant conditions, may need to undergo surgery under general anaesthesia, but the impact of the assumed suppression of the HPA axis has not been determined. It is possible that there is another unknown mechanism that supports such patients and prevents catastrophic adrenal insufficiency and crisis, but this remains highly speculative. Likewise, does the use of potent opiate analgesic pre-medication compromise surgical survival? These are important questions which until now have been rarely considered and discussed, and the present publication is an important landmark study that such considerations are now being taken seriously into account. The authors do point out the difficulties in recruitment for this type of study, but clearly the topic is worthy of more extensive investigation. It would be of great interest to recruit a much larger cohort over time, and with a well-annotated cortisol assay it may not be necessary to run a parallel control group, while an ACTH stimulation test may be adequate without any further dynamic stimulation. We may have thought that we knew most of there was to know regarding the clinical assessment and treatment of changes in the HPA axis, but there still appears to be much to learn in the 'opiate story', suggesting we are just seeing the tip of the iceberg.

Declaration of interest

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