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Discontinuing opioids in a safe way. Case report and recommendations for Palliative Care

Abstract

Opioids are the mainstay of pain treatment in cancer. In the course of disease many patients will experience increase of pain intensity and hence need an increase of the opioid dose. However, in some situations, when for example the other treatment of pain is effective, the dose of opioids could and should be decreased or even discontinued. Many patients continue on the opioids because it is unclear how and when to discontinue them. We present the case of a patient treated for his pain with opioids. Opioids were responsible for vivid delirium, probably exacerbating subclinical dementia. Treatment with steroid injections allowed to decrease and later discontinuation of opioids with a clear gain in lucidity and cognitive functioning by the patient. We propose the guidelines how and when to wean patients from the opioids. Buprenorphine and clonidine, but possibly also gabapentin may play a role in the prevention and pharmacological treatment of the symptoms of abstinence.

Key words: opioids, pain therapy, discontinuing opioids

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Introduction

Opioids continue to be the mainstay for pain relief in palliative care [1, 2]. They are usually used in combination with other drugs and their dose should always be titrated to the effect. When the pain is under control with other modalities the dose of opioids can and should be decreased or sometimes even discontinued. Patients may also sometimes wish to discontinue opioids, most often due to their annoying adverse effects. Also it could be the case that patients want to get off opioids due to the fear of addiction and/or dependence. However, in many instances patients with advanced disease will be continued on opioids even though they do not require them any more, simply for the sake of convenience, due, primarily to concerns relating to adverse withdrawal effects. Discontinuation of opioids may induce pain, a condition defined as opioid induced hyperalgesia, for a short period of time which affirms to the patients and their doctors in the conviction that they certainly need opioids [3–5]. This can result in unnecessary long term adverse effects and considerable costs.

The guidelines for initiating opioid treatment are well recognised and accessible; however there is no consistent guidance for stopping the treatment. The major concern with stopping opioid use is the withdrawal syndrome that can develop within hours [5].

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The symptoms are not necessarily life threatening, but can be very distressing, especially within the sensitive settings of Palliative Care. Signs and symptoms of opioid withdrawal are those of sympathetic over activity, and include tachycardia, tachypnea, irritability, gastrointestinal symptoms, vomiting, diarrhoea, abdominal cramps, insomnia, anxiety, muscle spasms, and skin hyperalgesia. Unrecognised, these symptoms may lead to the conclusion that the patient is again in pain and needs recommencing of opioids.

Issues to consider are the time-frame of how acutely the opioid treatment is to be discontinued and also to take into account the individual case. The goal should be to allow the patient to be opioid free as quickly as possible with the least effects of withdrawal or precipitation of any other conditions. It would be difficult to set a given time frame as factors such as age, prognosis, comorbidity, kind of drug, duration and dose used and the patient's psychological status all need to be taken into account. There is probably no point to discontinue opioids in somebody who is in his last weeks of life.

To illustrate the issue we want to present the following case.

Mr A. was an 82 years old widowed man. He was a retired military officer and his hobby was to take care of retired greyhounds. He was well cared by his daughter Jane (60) who lived next door to him. Jane was single and partially disabled as she has had poliomyelitis in her childhood and walked with a stick. Mr A. was diagnosed with locally advanced prostate cancer two years before. There were no metastases and he was treated with transurethral resection and curative radiotherapy to the prostate. After this treatment he recovered fully and was able to function alone at home. His prostate specific antigen (PSA) initially increased, then dropped to the normal values after radiotherapy. Eight months before there was one abnormal high PSA value which prompted his urologic surgeon to commence with hormonal therapy. The bone scan repeatedly did not reveal any hot-spots and the next readings of the PSA were again normal. He continued on hormonal therapy but started to forget things. He was sometimes agitated, especially in the evening. His GP requested formal assessment for his dementia as he expected that he will need a placement in a psychogeriatric nursing home. This assessment revealed mild dementia. Two months before, he started to complain of pain in his lower back which did not respond to paracetamol and NSAIDs. He was started on oral morphine which was titrated to 30 mg bd and later changed to fentanyl patches 25 and a week later to 50 mcg/hour. His pain was better controlled with this treatment but still present, urging him to use the oral morphine rescue doses of 10 mg, sometimes 3–5 times a day. He became also constipated and struggled with his laxatives as he was terrified by the idea of soiling the floor before reaching the bathroom. He was not sleeping well, was agitated at night and still suffering the pain. He was admitted for pain control to our hospice but needed to be discharged because of aggression and difficulties with the nursing staff. His daughter did not want to admit him to the psychogeriatric nursing home and took him back home. The consultant (ZZ) visited him at home. He still appeared to have a normal PSA and no signs of bone metastases. He suffered from severe localised pain at his iliac crest on the right side [6]. There were three trigger points corresponding to the upper cluneal nerve, cutaneous branch of the iliohypogastric nerve and cutaneous branch of the subcostal XII nerve crossing the iliac crest. The three sites were injected with bupivacaine and methylprednisolone. The next day he was free of pain, but much more confused. The fentanyl patch was decreased to 25 mcg/hour and later swapped to buprenorphine patches 20 mcg/hour. As he was still without pain a week later, the dose was again decreased to 10 and a week later to 5 mcg/hour. Seven days after commencing him on buprenorphine 5 mcg/hour the patch was removed. He was prescribed clonidine 0.1 mg tablets to be taken in case of withdrawal symptoms, but he never used them. He recovered fully after this and could stay at home for another seven months. He was not confused and the injections were repeated regularly every 3 months until his death because of massive stroke.

Discussion

Patients with dementia are particularly sensitive to opioids [7]. Even small doses of these drugs may totally deregulate them; make them confused and sometimes aggressive. Obviously the pain should be treated effectively and when needed with opioids. However, particular effort should be taken to intensify all non-opioid pain treatments to avoid drug toxicity. Radiotherapy to painful bone metastases, nerve blocks, and also the addition of pregabalin/gabapentin to the treatment regime are just some examples of such treatment. They all may result in a decreased need of opioids and in some cases opioids

can and should be fully discontinued. There is a scarcity in the literature on weaning patients from opioids, other than non-cancer opioid addicts.

Buprenorphine is an opioid with a high affinity for opioid receptors. It has a partial agonist action on the mu receptor and antagonistic effect on the kappa receptor [8]. The affinity to both of these receptors is high and buprenorphine potentially may displace agonists from opioid receptors. Buprenorphine is used as a potent opioid analgesic in cancer care [8–10] but can also be used as a drug of choice in weaning patients addicted to opioids [11, 12]. The drug is slowly dissociating from the receptors providing their continuous occupation with less than maximal stimulation (partial agonism). This results is a marked reduction in craving and other withdrawal symptoms.

In clinical trials, buprenorphine has been found to be more effective than clonidine [13]. Due to it being a partial agonist rather than a full agonist, it is safer to titrate down the dose more rapidly than normal opioids. The slow dissociation of buprenorphine from the opioid receptors causes fewer withdrawal symptoms on discontinuation. Recommendations for buprenorphine treatment are presented in Table 1.

Buprenorphine is available as a transdermal patch in strengths of 5, 10 and 20 μg/h (Butrans) and 35, 52.5 and 70 μg/h (Transtec). The ideal medication for transdermal administration should be highly lipophilic, potent and of low molecular weight for ease of crossing the skin barrier [15]. Buprenorphine meets all of these requirements.

Preliminary data from a survey of 3,255 patients with chronic pain who had used a transdermal buprenorphine product indicated that the incidence of side effects was relatively low compared to other opioids [16]. Long-term use of buprenorphine administered as a transdermal patch (mean exposure time 234 days, range 1–609 days) in approximately 400 patients with chronic pain in a clinical trial showed no unexpected safety concerns [17]. Also the dose of the drug remained very stable in comparison to what is known about other opioids.

In the palliative care setting the transdermal patch is much more advantageous over sublingual therapies for a number of reasons. Patches provide smoother, more continuous drug delivery, offering steadier plasma levels of the opioid, and can have less side-effects. With the patch being more patient and carer friendly it can lead to better compliance. Patients in Palliative Care tend to be frail and struggle with medication and therefore a patch can provide ease of delivery.

The risk of lethal overdose on buprenorphine in an opioid tolerant individual is less than that associated with the use of other opioid medications. This is due to the ceiling effect concerning the respiratory depression but not analgesia [18].

Before buprenorphine patches, withdrawal symptoms were treated with clonidine [19, 20]. Oral clonidine 0.1–0.2 mg 4–6 hours as needed or by transdermal patch (Clonidine transdermal 0.1 mg/24 hour patch which provides 0.1 mg a day for 7 days) can be used to treat autonomic hyperactivity symptoms.

Clonidine is a centrally-acting α-adrenergic receptor agonist. It selectively stimulates receptors in the brain that monitor catecholamine levels in the blood. These receptors close a negative feedback loop that begins with sympathetic nerves from the brain that controls the production of catecholamines in the adrenal medulla. Clonidine causes the brain to reduce its signals to the adrenal medulla, which in turn lowers catecholamine production. The result is a reduction in sympathetic activity causing a lowered heart rate and blood pressure, with side effects of dry mouth and fatigue. If clonidine is suddenly withdrawn the sympathetic nervous system will revert to producing high levels of catecholamines, potentially causing a rebound reaction. This is relevant to the treatment of hypertension with clonidine but can be avoided by slowly withdrawing treatment.

The major drawbacks of clonidine therapy are the adverse effects: hypotension and dry mouth. Measurement of blood pressure prior to commencing therapy in patients with advanced disease is necessary.

Table 1. Recommendations for buprenorphine treatment

Try to reduce the dose of original opioid as much as possible;
Swap patient from the last dose of original opioid to buprenorphine pathches using the equianalgesic dose tables [14];
Decrease the dose of buprenorphine patch once per week, decreasing it by 10 and later 5 mcg/hour;
Have clonidine 0.1 mg tablets "stand by" when the last patch is taken off;
The length of this process depends on how long the original opioid was used. The shorter this period was, the shorter weaning off can be.

In the recent years gabapentin and probably also pregabalin emerged as a drug able to control the withdrawal symptoms [21, 22]. There is only little experience with these drugs in this context, but because of their frequent use in palliative care, potentially, they may play an important role.

Other agents should be considered if required and their use depends on the withdrawal symptoms that arise:

— diphenoxylate/atropine or loperamide to treat acute diarrhoea;
— hydroxyzine for anxiety and sleep problems;
— trazodone, zolpidem, temazepam. Used for anxiety, depressive illness, requiring and sedation;
— dicycloverine hydrochloride for gastrointestinal disorders;
— non steroid-anty-inflammatory drugs (NSAID's) for pain relief.

Conclusion

Currently there are no standard protocols for discontinuing opioids in Palliative Care due to the fact that this is an uncommon practice. However, some guidelines can be extrapolated from other disciplines. Regardless of the reason for the discontinuation, the plan must be individualised to each patient's needs. Close follow-up and psychosocial support are essential. Buprenorphine is an established, effective and safe medication for use in the treatment of opioid dependence and with its unique pharmacological profile it can, in theory, be used in limiting adverse effects of withdrawal from long term high dose opioid therapy in Palliative Care, thus making it a safer and steadier process for the patient.

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