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Differentiating neuropathic pain, opioid–induced hyperalgesia and opioid tolerance; considerations following a remarkable case

Abstract

Most of the problems in pain control in end of life care are encountered due to three main syndromes or their combinations: neuropathic pain, opioid-induced hyperalgesia and opioid tolerance. In this article, we discuss a patient who was no longer responding to opioids and suffering severe pain, while the opioid dose was very high and still rising. It may be apparent that the three syndromes have a lot in common and their differentiation is not straightforward. However, guidelines can be given for differentiation and a rational approach to treatment.

Key words: neuropathic pain, hyperalgesia, opioid induced hyperalgesia, opioid tolerance, cancer pain

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Introduction

In palliative care it sometimes happens that pain rapidly exacerbates and that even high doses of opioids do not provide adequate analgesia. At that point, it is important to go back to basics and first try to understand the nature of the pain, to put the facts in a row and try to interpret the situation using definitions and evidence. Not infrequently there is not much time to do this, as the patient's suffering is overwhelming and the pressure on the doctor "to do something" is very high. Increasing the dose of opioid once more is not usually the answer. In cases of severe pain exacerbation, a couple of syndromes should be considered.

First of all, the patient may have a pain that does not respond well to opioids. Neuropathic pain is a classic example of this and this pain may be only partially opioid responsive [1, 2]. This type of pain may respond to a certain degree but a further increase will not improve analgesia. Secondly, the patient may suffer from opioid-induced hyperalgesia (OIH), which is a relative newcomer in palliative care but is probably more common than we previously thought [3, 4]. Opioids, besides their inhibitory effects on pain transmission, may at the same time interact with Toll 4 receptors in the spinal and brain glia and induce pain, facilitating an inflammatory response [5, 6]. Thus, with this syndrome, the more opioids given, the more pain is produced. The third syndrome is that of opioid tolerance, when pain is still responsive to opioids but the doses to obtain this effect are becoming higher and higher [7]. All three of these syndromes overlap each other in many

ways and may be accompanied by similar adverse effects. From the clinical point of view it is essential to differentiate these three syndromes, as the treatment of pain in each case is different.

In this article we try to differentiate these three syndromes using a clinical case. We also try to propose a rational approach to the treatment of each one.

A man (aged 59) was diagnosed a year earlier with a poorly differentiated non-small cell lung cancer. There were no distant metastases but the disease was locally advanced with tumour growth in mediastinum. The patient underwent intensive radiotherapy which was complicated by myocardial infarction. While waiting for funding for erlotinib therapy, he experienced severe pain in his back and was treated, initially with success, with controlled-release morphine sulphate 60 mg bd. However, in the course of two months the dose of controlled-release morphine sulphate was increased to 460 mg bd. Besides this, he was taking 30 mg of oral morphine 4–6 times daily, usually with some pain relief which persisted for 3–4 hours. Altogether, the morphine sulphate dose averaged 1100 mg daily. He did not, apparently, develop constipation while taking these high doses of morphine. Other medication consisted of paracetamol 4 g a day and amitriptyline 10 mg nocte. The dose of the latter drug was kept low because of the history of myocardial infarction. With this medication the pain gradually became worse. He experienced severe hypersensitivity to pinprick, especially on his back (Figure 1). He was admitted to the ward for a swap from morphine to buprenorphine; buprenorphine was started in patches at the dose of 70 μg/hour. He was still allowed to use immediate-release morphine sulphate, 60 mg per dose at that time. Not surprisingly, he only used the extra doses of morphine occasionally and the amount was decreased later to 30 mg per dose. Later the dose of controlled-release morphine sulphate was gradually decreased to 90 mg bd. In expectation of neuropathic pain being the main problem, oxcarbazepine 150 mg bd was added to his medication. At this time the patient felt much better and asked to go home. His pain was much better controlled, but still present. He was discharged with the possibility of using the 30 mg extra dose of morphine sulphate when needed and was scheduled to be seen in the clinic two weeks later. However, for no apparent reason, he did not show up until a month later, when he was again in severe pain. The dose of controlled-release morphine sulphate was increased again by the

Figure 1. The area of hyperalgesia (marked with pen) is diffuse and does not correspond with distribution of any known nerve

general practitioner to 180 mg bd, and the patient was using 8 doses of immediate-release morphine sulphate 30 mg (total daily dose: 600 mg). Above all he started to complain of a local reaction to the buprenorphine patches and needed to discontinue them. After that the morphine dose shot up again and the pain became unbearable. He was admitted once more. On examination he appeared relatively well. There was marked hyperalgesia in the dermatomes T_2–T_8, right more than left. There was also marked allodynia present on the right side. Chest compression from the sides and front-to-rear was not painful, suggesting that the pain was not due to bony involvement. An abdominal ultrasound did not reveal any organ pathology.

At that stage oxcarbazepine was discontinued as being completely ineffective. Diclofenac 50 mg tds was started and this brought a massive improvement in the pain. This allowed us to decrease further the dose of morphine sulphate and he was swapped to methadone, allowing morphine sulphate 10 mg to be used as a rescue medication. The dose of methadone was titrated up to 50 mg bd. The quality of analgesia improved dramatically but the patient

became constipated for the first time and needed laxatives.

At this time the patient also started to take erlotinib 150 mg od and began to experience a mild skin rash because of this drug. Six weeks later a progression of the tumour was diagnosed and erlotinib was discontinued. The patient remained pain free using a combination of an increased methadone dose of 80 mg bd, diclofenac and occasionally immediate-release oral morphine 10 mg.

Discussion

Our patient suffered from pain that initially responded to opioids. The distribution of the hyperalgesia did not correspond with the potentially damaged neurological structures and could not be described with dermatomes. The pain gradually increased and very high doses of morphine were administered. The patient reported that each dose increase gave some relief for a short while, which was why the dose of morphine increased so swiftly. The patient was treated with oxcarbazepine but did not experience any improvement. While this fact is not strictly differentiating, it makes neuropathic pain less probable. Neither did the original pain description suggest that there was neuropathic pain before the start of the opioid treatment. Was this, therefore, a feature of the rapid progression of tolerance or OIH? It is important in answering this question to know what happens after a reduction of an opioid dose. In the case of OIH, the pain would improve, while in the case of opioid tolerance the pain would become worse. In the case of neuropathic dose reduction, this would not at first have any effect on the pain, but total discontinuation of opioids could induce a worsening of the pain. In our patient, a massive reduction in the opioid dose resulted in pain improvement; however, we were not able to or did not pursue the complete discontinuation of opioids. The lack of characteristics of neuropathic pain suggested to us that our patient was suffering from OIH.

However, the patient responded swiftly to a dose decrease and the introduction of diclofenac, while the normal doses of paracetamol were not able to change the clinical outcome. Paracetamol may be effective in the treatment of hyperalgesia caused by low doses of opioids [8] but it appears to be ineffective when given with high and very high doses of opioids [9].

Opioid-induced hyperalgesia differs from opioid tolerance in the shift of the dose-response curve in two different directions (Figure 2). In opioid toler-

ance the shift is to the right, but there is no specific pain facilitation. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in a decrease of the drug's effects over time. Many processes may contribute to this adaptation. Among them, the most important seem to be desensitization and the down regulation of opioid receptors [10]. On the other hand, OIH involves a number of mechanisms that facilitate pain, hence the shift of the dose-response curve downwards and a decrease in the pain threshold [11]. It is believed at the moment that morphine and other opioids may have an agonistic effect on the TLR4 receptors on the surface of the spinal microglia. Diverse drugs are able to interact with the TLR4 receptor and initiate a pro-inflammatory and pro-nociceptive response [5]. Most interesting is that morphine-3-glucuronide, a morphine metabolite thought to be inactive as it cannot bind to classical opioid receptors, is able to interact as an agonist of the TLR4 receptor [12]. The active morphine metabolite, morphine-6-glucuronide, is devoid of this activity [12]. The inflammatory response can be inhibited by the effect of NSAIDs; in the case of our patient, diclofenac [13, 14].
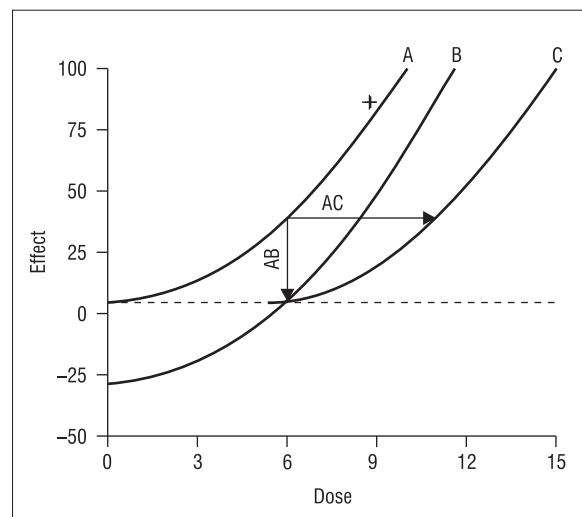

Figure 2. Tolerance and opioid-induced hyperalgesia (OIH) are pharmacologically distinct phenomena that share the same net effect on dose requirements. Either condition necessitates dose escalation for maintaining a certain drug effect. If tolerance is expressed, decreased drug potency is reflected by a right-shift of the dose versus effect relationship (AC). If OIH is expressed, increased pain sensitivity is reflected by a downward shift of the dose *versus* effect relationship (AB). Both tolerance and OIH result in the decreased effectiveness of a given drug dose (X). Modified from [31]

The treatment of pain in each of the three syndromes is different. In the case of neuropathic pain there is not much of a rationale behind treating the pain with opioids alone. Opioids should be titrated up until a flattening of the dose-response curve is obtained [2]. Other drugs, with more specific effects on neuropathic pain, should be added, the most common being carbamazepine or its congener oxcarbazepine [15]. However, carbamazepine may inhibit UGT2B7 glucuronyl transferase, thus inhibiting the metabolism of morphine to morphine glucuronides [16]. Oxcarbazepine, at least in mice, increases the anti-nociceptive effect of morphine and decreases morphine tolerance [17]. Gabapentin and pregabalin are frequently used, besides carbamazepine and oxcarbazepine [18–20]. The addition of NSAIDs is frequently used in the treatment of neuropathic pain, although no firm evidence exists to support this [21].

Opioid-induced hyperalgesia should mainly be treated through dose reduction [4] and the addition of drugs such as non-steroidal anti-inflammatory drugs and/or antagonists of the NMDA receptor, ketamine [22]. TLR4 receptors are sensitive to ultra-low

Table 1. Differential diagnosis of neuropathic pain, opioid-induced hyperalgesia and opioid tolerance

	Neuropathic pain	Opioid-induced hyperalgesia	Tolerance
Definition	Pain initiated or caused by a primary lesion or dysfunction in the nervous system. Pain in the area of altered sensation	OIH is a paradoxical response to an opioid agonist, whereby instead of an analgesic or anti-nociceptive effect occurring, there is an increase in pain perception	Progressive lack of response to a drug thus requiring increased dosing
Nature of the pain	Pain sensations in the distribution of the damaged neurological structure; i.e. pain in the area served by the damaged nerve or neurological structure. The area of neuropathy may show hyperalgesia and/or allodynia	The original pain may be well controlled or exacerbated. OIH pain may be much more diffuse and cannot be explained by the neuro-anatomical distribution, i.e. in dermatomes. In the area of OIH there may be hyperalgesia or allodynia	Pain sensitivity is unaltered; the original pain may still be present or be well controlled
How fast can this phenomenon develop?	Usually a couple of weeks or months after nerve damage	May develop rapidly, within hours or days	Usually develops slowly in weeks or months
Benefits of increasing the opiod dose	With increasing doses of opioids, there is usually an increase in adverse effects but no improvement in analgesia	Single/acute dose may be experienced as beneficial, although increasing the total dose of opioids does not usually result in pain improvement. Patients can usually state that, for example, doubling the dose of opioids did not improve the pain and if anything made the pain worse	Increasing the dose has a beneficial effect for a longer time, i.e. patients start on a dose of fentanyl 25 μg/ hour and after a couple of weeks this increases to 37.5 μg/hour, still without adverse effect and with adequate control of pain
Quality of pain	Usually burning, lacerating or stabbing	Usually different from the original pain. May have a character of sensitivity to touch or slightly painful stimuli	Unaltered in comparison to the original pain condition
Pain sensitivity	Increased	Increased	Unchanged
Pain threshold	Decreased	Decreased	Unchanged
Opioid adverse effects	Usual opioid adverse effects, indicating overdosing	May be accompanied by other symptoms of neurotoxicity: agitation, delirium, multifocal myoclonus, seizures	Usual opioid adverse effects, indicating overdosing
Initial response to opioids	Pain improvement up to a certain level; further increase in the opioid dose does not result in better analgesia	The pain may initially respond to opioids; however, it may also immediately get worse after starting opioids	Pain usually responds well to opioids
Effect of dose reduction	The pain will increase	The pain will decrease	The pain will increase

doses of naloxone and naltrexone [23]. Ultra-low doses of naloxone and naltrexone are found to be effective when administered together with opioids [24–26]. New combination preparations are currently undergoing clinical trials.

Opioid tolerance can be treated with increasing doses of opioids, providing the speed of development of the tolerance is not too high and the patient's prognosis is short. However, as cancer patients tend to live longer, this approach will no longer be sufficient in many cases. Switching to other opioids may counteract opioid tolerance, at least for a while [27–29]. However, evidence for this procedure is still very scarce [27]. Another approach may be the combining of opioids [30]. However, because of an outdated paradigm that "all opioids are similar as they act on the mu-opioid receptors", we have never seriously considered this possibility and the data are absent.

One last remarkable, and still unexplained feature in this case was complete lack of constipation despite very high doses of morphine. Later, after swapping him to methadone, he became constipated. We do not know the true meaning of this fact. It is possible that some opioid receptors do not accept morphine but are able to interact with other opioids.

Conclusion

Our patient suffered from severe pain most probably because of OIH. There were insufficient arguments to label this pain as neuropathic. Elements of opioid tolerance were also present. OIH and opioid tolerance share some characteristics. However, a reduction of the opioid dose may be a factor that will differentiate between them. The patient was successfully treated with morphine switched to methadone and the addition of diclofenac.

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