Case report

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A patient with intractable pain on high dose opioid therapy. Could we manage not to escalate the opioid dose?

Abstract

Prolonged opioid treatment reveals problems, like opioid tolerance and opioid induced hyperalgesia. On every stage of disease it should be remembered to use procedures that can have opioid dose sparing effect. We describe a patient with severe mixed neuropathic and nociceptive pain who despite complex medication embracing high dose of morphine suffered from untractable pain. He responded to opioid antagonist with sequential opioid rotation and a simple minimally invasive procedure.

Key words: mixed cancer pain syndrome, opioid induced hyperalgesia, opioid rotation, opioid antagonist

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Introduction

Most of the cancer pain responds to simple pharmacological and non-pharmacological treatments [1]. In the past, when the patient did not achieve satisfactory analgesia with opioid, its dose was sequentially increased with the conviction, that for the full agonists the relationship dose — effect is linear [2].

However, few patients never fitted into this paradigm. Parallel to advancement in oncology, patients with cancer live longer and symptoms caused by disease and treatment become more complex. Therefore many patients are much longer exposed to painkillers. Prolonged opioid treatment reveals problems, which previously didn't have chance to evolve, like opioid tolerance and opioid induced hyperalgesia (OIH). They are much more common nowadays than previously thought [3]. The awareness of different mechanisms responsible for diminished efficacy of analgesics and need of specific interventions is crucial for effective symptom control. On every stage of disease it should be remembered to use procedures that can have opioid dose sparing effect. We describe a patient with severe mixed neuropathic and nociceptive pain who despite complex medication embracing high dose of morphine suffered from untractable pain. He responded to opioid antagonist with sequential opioid rotation and a simple minimally invasive procedure.

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Case description

Fifty seven years old male with hormonally inactive left adrenal gland cancer and multiple bone and liver metastases was admitted to Hildegard Hospiz due to intractable severe pain in spite of multimodal management.

One year earlier after primary tumor excision the patient was treated with palliative chemotherapy (Carboplatin and VP16) and radiation therapy (46 Gy) to the area embracing tumour lodge, metastases in lumbar vertebrae L_3 and in iliopsoas muscle. That improved pain control. Couple months later, due to progression of metastases the patient received sunitinib, and later doxorubicin with mitoxantrone. One year after diagnosis he started to complain of progressive pain in the right arm and right cervical area. Computed tomography revealed osteoblastic metastases in the humerus and in the spine on the level of C7, Th6, Th12 and suspected lesions in T9-T11with the compression of the spinal cord. He had been treated with localised radiotherapy to cervical area (20 Gy), but to no avail. Due to severe pain and poor general condition he was evaluated as being ineligible for any further diagnostic or therapeutic procedure and referred to hospice. On admission the patient complained of pain in the right arm and neck area with concomitant right arm paresis. The pain localisation and quality (burning, with mechanical allodynia) suggested brachial plexopathy. Another mixed neuropathic and nociceptive pain was localised in left lumbar area. It was described as dull ache aggravated by and resolved with sitting up in twined position to the left. According to its characteristics, the pain was suspected to be caused by iliopsoas infiltration.

Pharmacological treatment of pain (localised in lumbar area at that time) had been started 9 months earlier with transdermal (TD) fentanyl. Over time, stepwise dose escalation were needed to keep the pain under control. Four months before hospice admission patient experienced acute pain crisis (10/10 on the NRS) despite continuing previous medication. He was admitted to hospital and fentanyl, at that time 300 mcg/hour TD, was switched to morphine administrated as a continuous infusion via central venous port (CIVI). On discharge its dose in infusion was 600 mg/24 hour, with couple of rescue doses of 100 mg (total daily dose, calculated as oral dose, maximally 2400 mg/day). In subsequent weeks a new pain in right brachial and cervical regions, emerged. Many analgesics and co-analgesics had been introduced, but with no success. The 10 days trial with oral corticosteroids was not effective either. Despite escalation of morphine dose the patient was still suffering severe pain, which was the direct indication for admission to hospice. The full treatment, immediately before hospice admission is given in Table 1.

Table 1. Treatment on hospice entry

	Daily dose
Morphine HCl i.v. in CAD	672 mg continuous infusion + boluses 1000 mg
MST Continuous	1200 mg
Pregabalin	450 mg
Celecoxib	200 mg
Metamizol*	4.0 g
Paracetamol*	6.0 g
Mirtazapine	30 mg
Lorazepam	1 mg
Pantoprazol	40 mg
Natrium picosulfat	5 mg

*The administered daily doses excide current recommendations

Due to severe pain in spite of increasing doses of morphine, with a previous history of high dose fentanyl administration, the diagnosis of OIH and/or opioid tolerance was proposed. It was decided to switch morphine into methadone and to start with a short term ultra low dose naloxone infusion. The significant improvement in pain control was achieved within two hours after naloxone 0.002 mcg/kg/min = 0.18 mg/24 hours) infusion was started. After stable pain improvement was established on naloxone, oral methadone was introduced with intention of stepwise morphine replacement. The patient was allowed to continue with morphine rescue doses as previously, but whilst on naloxone infusion, he hardly used them at all. At that moment the morphine dose to be swapped to methadone was equivalent to 3200 mg oral morphine (= sume of Morphine Doses administrated as oral MST cont. and intravenous boluses). As OIH was suspected, oral methadone was started 10 mg as needed every 3 hours. The patient had been asked to use the IV morphine rescue doses (from CADD pump) as little, as possible. In the second day, the pain intensity decreased and naloxone was discontinued. Then methadone dose was increased to 20 mg as needed every 3 hours, while slowly reducing regular dose of morphine until discontinued on day 13th (Table 2). The methadone dose was titrated up to 480 mg per 24 hours (in 4 separated doses) which appeared to help well for the pain. Whilst on

Table 2. Opioids doses and pain intensity in switching period

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
MF (as oral dose)	4500 mg	3500 mg	1344 1600	1344 + 1300	1344 + 1000	1344 + 600	1000 + 200	1000 + 500	1000 200	600 + 200	600 + 300	400 + 0	300+ 300	200 + 300	0 + 200	0 + 100
Methadone	0	50	90	120	150	220	290	230	390	430	500	490	360	360	360	360
Naloxone		0.18	0.18	mg/24 h												
Buprenorphine TTS												17.5	35	35	35	70
Mean pain intensity (NRS)	10	10 → 2	2	4	4					5	6	4	3	2	2	1

methadone the patient started to complain of diarrhoea 15–30 minutes after administration of each dose. He tolerated methadone better when taking smaller every 3h doses. To lower methadone doses and avoid gastrointestinal side effects, buprenorphine TD 17.5 mcg/h was added and uptitrated to 70 mcg/h. As this appeared successful, methadone dose was stabilised at 360 mg and was changed back to a q8h regimen without gastrointestinal adverse effects. However, the patient was not completely pain free. Several painful spots were identified, and three most painfull of them were injected with bupivacaine and triamcinolon acetonide (15 mg and 40 mg, per point, respectively). This improved further the pain control, apparently not only in injected points but also pain in not injected spots . The patient went home, with a very good pain control. His medication at discharge is given in Table 3.

Parallel to methadone dose escalation stepwise prolongation of QT in ECG was observed (form 410 ms to 470 ms). The patient remained symptom free for 4 weeks. After that time his loss of energy hastened and general weakness started to progress more quickly than previously. Despite the lack of clear symptoms of acute suprarenal glands insufficiency, the probability of the deficit for glucocorticoids 4 weeks after triamcinolon administration was taken into account and prednison 20 mg p.o. was prescribed. A few days later the patient started to complain of pain in the same areas as previously. The dose of methadone was increased by 50% which allowed to achieve satisfactory pain control. After several days the general condition worsened. In the last phase, when oral administration was no longer possible, methadone was administered IV. According to patients' wishes he remained at home till the end.

Table 3. Medication on discharge

Methadone 120 mg every 8 hours
Transtec TTS 70 mcg/h every 96 hours
Paracetamol 1.0 QDS
Pregabalin 300 mg TDS
Diclofenac SR 100 mg OD
Pantoprazol 40 mg OD
Mitrazepin 30 mg OD
Lorazepam 1 mg PRN
KCl retard drag. 8 mmol OD
Magnesium solution 5 mmol OD
Rescue medication:
Methadone *p.o.* 80 mg — PRN
Morphine hydrochloride 50 mg *i.v.* via central venous port — PRN

Discussion

Many factors might contribute to opioid dose escalation including cancer progression, new pain components, pharmacokinetical disturbances (f.ex. in opioid absorption or drug-drug interactions), psychological causes (anxiety, depression) and opioid tolerance or OIH. In case of the patient presented here none of those factors could be absolutely excluded. And this is not such rare situation especially in hospice environment where the details about tumour progression for obvious reasons were often difficult to obtain. However analysing history and the clinical picture we thought that the most important factor responsible for need to increase opioid is the OIH syndrome. Interventional techniques should have to be considered as they could effectively improve pain control. However, their implementation would require further examinations (f.ex. MRI) and time. Whilst the pain intensity was so high and the prognosis so short term the effective pain control was urgently needed without any delay.

There is a lack of studies investigating how often OIH is the cause of pain exacerbation among patients with advanced cancer. Its diagnosis in hospice patients is more difficult especially when OIH is seen as exacerbation of previous pain. Much more typical for OIH and easier to be recognised is appearance of

Table 4. Postulated mechanisms of OIH [4, 5, 11, 12]

Molecular level
1. Changes in opioid receptor conformation (switching coupling with Go/i to Gs)
2. Stimulation of calcium/calmodulin-dependent protein kinase II (CaMKIIalfa)
3. Stimulation of opioid receptor-like receptors (ORL-1)
Neuroanatomical level
1. Sensitisation of peripheral nerve endings
2. NMDA mediated (reflex increase in downstream stimulation of NMDA receptors which facilitate nociceptive stimulus transmission)
3. Spinal dynorphine transmission
4. Enhanced production, release or diminished reuptake of nociceptive neurotransmitters
5. Sensitisation of second order neurons to nociceptive neurotransmitters
6. Activation of toll-like receptor 4 (TLR4) expressed by glia

diffuse allodynia (central sensitisation) not-associated with previous tissue damage [4, 5]. On the contrary several reports suggest that OIH embrace diminished pain threshold (hyperalgesia) but not allodynia [6]. In the simplest approach (but it is probably too simply) OIH should be suspected if not satisfactory controlled pain worsened after opioid dose escalation [5]. In fact, more often in OIH morphine dose elevation improves pain only temporarily, making the dose escalation apparently helpful. The need for next dose escalations is usually misinterpreted as simple tolerance to opioids or disease progression and the idea to diagnose OIH is not taken into account. The exact molecular mechanisms of OIH remain still area of speculations and were discussed in this Journal previously (Table 4) [7].

The data about OIH in patients with cancer pain are scarce, but the problem seems to be more important than previously thought [3]. The broad introduction in daily practice of quantitative sensory testing could help to determine the OIH prevalence in cancer patients. Currently it is hypothesised that risk to develop OIH depends on dose and duration of opiod treatment and the drug used. However the frequency how often OIH seen, described depends on the test used to diagnose it [4].

There are two main arguments for diagnosis of OIH in our patient: 1/ rapid answer to ultra low dose of naloxone, and 2/ better efficacy of opioid with more anti-hyperalgesic activity (methadone) compared to morphine [5].

From two mostly often mentioned drugs to treat OIH (buprenorphine and methadone) we decided to use methadone, because of the morphine dose to be replaced was so high, that it was unrealistic to hope to reach this with buprenorphine patches. However the role of methadone in OIH treatment still remains the controversial [5].

In our patients morphine boluses where effective all the time, and, what is very interesting, their effectiveness increased after switching to methadone. We didn't observe worsening of pain after morphine at any moment.

However, the dose of methadone needed to control pain, comparable with previously used huge morphine dose, votes against pure OIH in described patient. Improvement of methadone effectiveness wasn't observed after morphine discontinuation. It suggest that accumulation of morphine-3-glucoronides (M-3-G) was not responsible for diminished opioid efficacy. NMDA receptor activation and M-3-G accumulation are supposed to play a role in patients treated with larger doses of morphine [5, 8], what can't be confirmed in our patient. Maybe additional mechanism of methadone as a NMDA antagonist could explain increased effectiveness of morphine given as rescue for breakthrough pain. On the very beginning of our treatment modification we observed clear improvement with ultra low dose naloxone infusion. It suggests that the OIH in given patient can be explained with bizarre coupling of OR with G protein. During exposition of opioid receptors with opioids they become coupled with stimulating instead of inhibiting G protein. Replacement of $G_{i/O}$ with G_s results in opposite intracellular signal transduction. In OIH opioids induce paradoxical cAMP elevation, instead of expected drop. According to this theory successful attempts to treat OIH with ultra-low dose of naloxone are described in the literature [9–11]. This intervention was successful in given case.

Buprenorphine might be more antihypergesic than other opioids due to its partial mu and ORL-1 agonistic activity as well as antagonistic effect against kappa and delta OR (on the other

hand, kappa receptor stimulation for example with dynorphin can evok OIH) [12]. These complex activities against different OR types are combined with interaction with different G protein (Gs and Go/i). One of growing hypothesis about mechanism of OIH is switching opioid receptor coupling with another type of G protein.

What could be done better? Considering 1.non-pharmacological methods of analgesia, however very difficult in the patient situation; 2. stronger NMDA antagonist, such as ketamine; 3. longer infusion of ultra low dose of naloxone; 4. earlier introduction of steroids — we believe that that beneficial effect on different pains (not only local) of depo steroids was partially dependent on the systemic action due to significant total dose of injected corticosteroids;

However, most of the time the level of analgesia was reasonable and we had impression that the patient did not suffer due to pain.

Conclusion

This patient was an example of severe and complex pain of mixed nociceptive and neuropathic origin. Simple treatment with opioids and adjuvants was not successful and the patient developed severe OIH. Ultra low dose of naloxone, swap of morphine to methadone and buprenorphine as well as the specific treatment of the pain due to peripheral nerve compression appeared to be successful and allowed patient to be discharged and to die at home. The key to the diagnosis and treatment of this patient was taking minute history of pain symptoms as well as attention to details.

Piśmiennictwo

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