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Opioid antagonists may be useful in control of intractable pain in advanced disease. A case series

Abstract

Opioid antagonists naloxone and naltrexone administered in ultra low doses are able to control pain which originates from opioid induced pain facilitation or hyperalgesia. In this article we describe a series of patients with intractable pain treated compassionately with ultra low doses of naloxone or naltrexone. Most of the patients suffered of advanced cancer disease and were treated with high doses of opioids. However, one patient suffered of non-malignant pain and did not tolerate exogenous opioids at all. She responded to ultralow doses of naloxone and naltrexone alone suggesting that endogenous opioids may also play a role in pathological pain conditions. Basing on this case series we discuss current literature, trying to make sense out of plethora of negative and positive findings.

Key words: opioid induced hyperalgesia, naloxone, opioid antagonists, pain, cancer

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Introduction

It is known for more than ten years that opioids may not only inhibit pain transmission, but also, alongside, cause pain facilitation [1–4]. This phenomenon is called opioid induced hyperalgesia (OIH). Numerous animal and human studies revealed that the mechanism of OIH is frequently related to the changes in opioid receptors from the inhibitory to the excitatory mode [5–7]. Opioid receptors in the excitatory mode are particularly sensitive to inhibition by picomolar while the opioid receptors in the inhibitory mode respond with inhibition to nanomolar concentrations of opioid antagonists [8]. Blocking of the opioid receptors in the excitatory mode can also be effectuated by cholera toxin [9] or inhibitors of neuraminidase [10]. OIH may be more common than previously expected [3, 11] and it may play an important role in development of tolerance to opioids [2] as well as in intractable pain [3]. Although this part of evidence is not controversial, the whole hypothesis was initially questioned by the variable and apparently contradicting results of clinical trials using combinations of opioids and ultralow dose of opioid antagonists [12–14]. The "ultra low dose" of opioid antagonists used was not well defined and positive effects were reported with the wide range of doses. However, negative results tended to be reported with relatively high doses of antagonists [15, 16], which could also revert opioid analgesia. Nobody performed dose titration studies for opioid antagonists. Other reason of this conflicting evidence may be the phenomenon described by Crain and Shen suggesting, counter intuitively, that patients receiv-

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ing higher doses of opioids may respond to lower doses of antagonists [8]. According to this idea, the doses of antagonists needed to counteract OIH may be variable not only from person to person, but also within one person when the doses of opioids inducing OIH are changed. In the clinical trial with large number of patients with ostheoarthritis using either placebo, oxycodone or oxycodone with two different doses of naltrexone, significantly improved analgesia was observed in patients receiving naltrexone twice daily but not four times daily and oxycodone immediate release twice daily [17]. As the duration of analgesia induced by oxycodone is short, naltrexone induced analgesia even in the absence of oxycodone in the blood. This raises the issue of opioid antagonists being analgesic per se in the low doses even without the use of opioid analgesics. Unfortunately, the authors did not involve a control group with naltrexone alone. The combination of oxycodone with fixed dose of naltrexone (Oxytrex) is patented and there is a lot of published and unpublished clinical data which will probably be released when the drug will obtain a license [18–20].

OIH can be experienced anywhere on or in the body, and may be confused with neuropathic pain [21]. It is sometimes complicated by signs of neurotoxicity like delirium and drowsiness [11].

Based on the review of the literature we postulated that some patients experiencing excruciating pain in advanced disease, despite high doses of opioids, may actually suffer of OIH. In the past seven years many patients experiencing this kind of pain were compassionately treated with ultra low dose of naloxone, 3 μg.kg^{-1}.24 h SC, according to the internal protocol. Here we present patients who contributed to our knowledge and experience. Several patients were treated by ZZ in the time he worked in the Netherlands. These observations combined with the data from literature should contribute to better understanding of the OIH phenomenon and help to develop future trial protocols.

Case no. 1

A man aged 40 with pre-B-AL leukaemia was discharged home after intensive treatment with chemotherapy. At discharge he had 25% of blast cells in his peripheral blood, thrombopenia and low back pain (intensity 8/10). His liver function was severely disturbed. The pain was treated with transdermal fentanyl 25 μg.h^{-1}. Initially the pain intensity dropped to 3/10, but a week later increased to 7/10. The fentanyl dose was increased gradually to 150 μg.h^{-1} over several weeks. Each upward adjustment of the dose of fentanyl was initially accompanied by improved pain relief but each time, after one day, the pain was no better than before. The patient became restless and confused at night. When admitted as an inpatient, he had severe abdominal pain in the right upper quadrant and pain in his lower back (intensity 9/10). A whole-body allodynia on light touch was noticed. While his fentanyl medication remained unchanged, a continuous SC infusion of naloxone 200 μg.24 h^{-1} (3 μg.kg^{-1}.24 h^{-1}) was started. After 4 hours pain intensity had decreased to 6/10, and after 24 hours to 2/10. The confusion cleared, and he returned home. The dose of naloxone remained unchanged and, although the pain remained controlled, the backache became a problem. Gabapentin 1800 mg/day successfully controlled this. He developed progressive paraparesis and paroxysms of high fever. He died without pain several days later.

Case no. 2

A man aged 74 with liver metastases from colon cancer developed jaundice which was accompanied by severe abdominal right upper quadrant pain (intensity 7/10), but no pruritus. A stent was introduced into the common bile duct, leading to a resolution of the jaundice. Because the liver pain persisted, he was prescribed oxycodone. The pain was relieved only partially by this, and for a few hours after each increase of the oxycodone dose. Within three weeks the dose reached 300 mg t.d.s. but the patient still scored the pain intensity 9/10. No cutaneous allodynia or hyperalgesia was noticed. Surprisingly he was not constipated and his pupils were not constricted. Visceral OIH was suspected and the dose of oxycodone dose was arbitrally decreased to 115 mg, t.d.s. A SC infusion of naloxone 200 μg.24 h^{-1} (3 μg.kg^{-1}.24 h^{-1}) was started The intensity of liver pain decreased to 4/10 within 3 hours but pain in the lower back and lower abdomen became more apparent (intensity 6/10). The naloxone dose was then titrated down to 166, 133 and 100 μg.24 h^{-1} (2,5, 2,0 and 1,5 μg.kg^{-1}.24 h^{-1}, respectively). At this level he was pain free. After 1 week being on naloxone, a trial of decreasing the oxycodone dose to 100 mg t.d.s. caused immediate liver pain increase. So the oxycodone dose remained 115 mg t.d.s. Because of irritation at the infusion site, he was switched to an oral solution of naltrexone 0.01 μg.kg^{-1} o.d. (water solution made from crushed 50 mg tablets). Naltrexone at this dose was well tolerated but, to achieve satisfactory analgesia, the dose needed to

be titrated up to 0.015 mg.kg^{-1} o.d. At this dose pain in both locations was totally relieved (intensity 0/10). The patient was able to work in his garden and enjoyed a short holiday overseas. After he returned he developed a gastro-intestinal obstruction which did not respond to standard medical management. He was sedated with drugs for his last three days.

Case no. 3

A woman aged 73 with known rectal cancer and liver metastases developed carcinomatous peritonitis and bowel obstruction, for which she underwent surgery. After this she developed a diffuse lower abdominal pain, treated with transdermal fentanyl 25 μg.h^{-1} and later 50 μg.h^{-1}. The lower abdominal pain decreased, but she started to complain of pain in the right upper quadrant (intensity: 6/10). While her fentanyl medication remained unchanged, a continuous SC infusion of naloxone 200 μg.24 h^{-1} (3 μg.kg^{-1}.24 h^{-1}) was started. After 3 hours the dose was lowered to 133 μg.24 h^{-1} (2 μg.kg^{-1}.24 h^{-1}) and the pain increased. Then the dose was adjusted to 233 μg.24 h^{-1} (3.5 μg.kg^{-1}.24 h^{-1}) and both types of pain decreased to 0/10. She remained pain free until her death three weeks later.

Case no. 4

A retired plumber aged 65 had a mesothelioma of the right chest which had spread to the peritoneum despite chemotherapy and radiotherapy. Pain was treated with increasing doses of oxycodone SR tablets. Eventually, the patient was taking oxycodone 1 g/day but, because he became drowsy and confused, the dose was halved. Surprisingly, this resulted in a marked reduction in the pain. After several weeks, the pain increased again, and was maximal in the right hypochondrium. A parallel increase in medication resulted in a return of the drowsiness and confusion, and the patient was admitted as an inpatient in order to switch from oxycodone to methadone. Methadone was titrated up to 20 mg t.d.s. but this only partially relieved the pain. Higher doses were not well tolerated. A SC infusion of naloxone 3 μg.kg^{-1}.24 h^{-1} was started, while the oxycodone remained unchanged. The pain decreased from 9 to 2/10. However, the respiratory rate decreased from 16/minute pre-naloxone to 4/minute eight hours later. Reducing the dose to 2.5 μg.kg^{-1}.24 h^{-1} gave better analgesia, but the respiratory rate decreased at night again to 4/minute. Because of continuing concern, naloxone was discontinued after three days. It was decided that, when the pain recurred, alternative treatment would be introduced. After 48 hours it became necessary to start a SC infusion of diamorphine 30–60 μg.24 h^{-1} combined with ketamine 200 μg.24 h^{-1}. Progressive sedation, but not analgesia, was achieved. The patient died a few days later.

Case no. 5

Female, 82 years old suffered in the past because disc prolaps with severe rheumatoid arthritis and osteoporosis. She was referred to anaesthesiologist because of severe pain in her thoraco-lumbar junction, experienced especially under her ribs. The vertebrae were tender on palpation and percussion and there was a marked hyperalgesia in the 12ths dermatome, more on the right than the left side. Before referral she was treated with a combination of Tramadol and Paracetamol. Epidural steroid injection had a doubtful effect and was not repeated. Oxycodone caused severe constipation. Fentanyl was titrated up to 75 μg.h^{-1} and was used together with low doses of oxycodone. Increase of Fentanyl helps every time for a while, but the beneficial effects wears off after several days. Besides pain the patient is hallucinating and agitated. Started with naloxone sc infusion 2 μg.kg^{-1}.24 h^{-1}. The next day the pain is much less and the patient notice "to be clear in her head". The pain is still present when she moves on the commode, but at rest she is as good as pain free. She starts with naltrexone 10 μg per day.

Case no. 6

A woman, 73 year old age suffered of severe pain due to bone metastases of breast cancer. Primary tumour was removed in 1993. She had undergone surgery and received radiotherapy afterwards. Ten years later she suffered severe pain and multiple bone-metastases were found on the bone scan. The X-rays showed pathological fractures of the pelvic bones. She was treated with radiotherapy. The patient become bed-bound and was admitted to the hospice. On arrival she was still in severe pain despite paracetamol 1000 mg q.d.s., diclofenac 50 mg t.d.s. and morphine controlled release tablets 30 mg b.d. Morphine sulphate immediate release 10 mg tablets were used frequently because of insufficient analgesia. Morphine was replaced by oxycodone controlled release tablets 30 mg, b.d. with Diclofenac and Paracetamol provided more adequate analgesia. Within several days, the patient started to complain

of restlessness, lack of concentration, forgetfulness and sometimes confusion, especially in the nigh hours. Especially confusion, she was experiencing as frightening and intimidating. So despite of more adequate analgesia her quality of life was poor and highly unsatisfactory. Addition of haloperidol and later olanzapine did not change the situation. Naloxone 5 μg.kg^{-1}.24 h^{-1} was started in a continuous SC infusion. The next day patient reported that her mind had cleared up greatly and she felt much better. Notwithstandingly her pain had worsened. Consequently the dose of naloxon was lowered to 3 μg.kg^{-1}.24 h^{-1}. The pain control improved again and after a few days the dose of Oxycodone could be reduced to 20 mg b.d. The patient remained clear. She became emotionally incontinent for a couple of days. She was crying and talking a lot. She discussed with her husband things that she would never discuss before. Four weeks later she told he doctor that this infusion, was the biggest miracle in her whole life and that we, doctors can never imagine how she suffered being in delirium.

Case no. 7

An otherwise healthy obese women aged 45 suffered since puberty from painful oedema on her legs. The subcutaneous tissue on both legs was always firm and tender. The pain was severe, continuous, and burning. Allodynia was apparent. Lymphoscintigraphy and Doppler examinations showed normal lymphatic and arterial circulation and only slight venous insufficiency in both legs. A diagnosis of lipoedema was suggested by a dermatologist. Paracetamol and NSAIDs did not relieve the pain. On several occasions she experienced poor tolerance of opioids (nausea and confusion) including tramadol, morphine, transdermal fentanyl and methadone. It seemed to her that the pain in her left leg increased whenever an opioid was prescribed. Ketamine-S, which she was using orally in the doses up to 30 mg daily was the only drug which was helpful. Because of its short supply, a trial of SC naloxone was undertaken. Naloxone 300 μg.24 h^{-1} (3 μg.kg^{-1}.24 h^{-1}) was administered as a SC continuous infusion in an n = 1 placebo-controlled double-blind trial (Figure 1).

Local pharmacy prepared two identical syringes, one containing normal saline, second naloxone. Two syringes were kept by the pharmacy in the refrigerator at +12°C pending the infusion. The trials took place on two days with one week washout in between. The patient was asked not to use ketamine-S for 24 hours before each infusion. During the first 6 hours vital signs were measured hourly. The pain scores were explained to the patient and assessed by her hourly. Six hours later she went home and continued infusion for up to 24 hours and continued to record pain scores. Saline, given during the first trial day, did not have effect on her pain. Three hours after starting the naloxone infusion the pain intensity decreased and reached 0/10 by bedtime. It remained 0/10until a few hours after the end of the infusion. Then the pain returned, and she needed to use extra doses of ketamine-S p.r.n. One week after the naloxone she started oral naltrexone solution 0.02 μg.kg^{-1} o.d. Although she experienced considerable relief within hours, the naltrexone needed to be titrated up to 0.13 μg.kg^{-1} over 2 months in order to keep her pain free. With this dose the pain remained largely controlled. Nevertheless she experienced frequent break-through pains which she was used to control with oral ketamine-S. Oral gabapentin up to the dose of 600 mg t.d.s. had no effect on her residual pain and was discontinued. At the time of writing, she has been taking naltrexone oral solution for 48 months. Naltrexone-induced bitter taste and anorexia have resulted in considerable weight loss (25 kg) — something she is still happy about, and definitely prefers to the pain.

Discussion

Opioid-induced hyperalgesia (OIH) is often referred to as part of opioid neurotoxicity [22]. However, the latter term disguises the fact that, depending on circumstances, exogenous opioids may activate either pain-facilitatory or pain-inhibitory systems. OIH was first described with high doses of morphine administered either intrathecally [23] or intravenously [24], and subsequently with oral medication [25]. OIH is also seen with other opioids, including ones structurally unrelated to morphine [26]. And, in this paper, cases are included where, seemingly, opioid-induced *visceral* hyperalgesia occurred in association with fentanyl and oxycodone.

There is no doubt that addition of ultra low doses of antagonists, both naloxone and naltrexone is able to decrease some but not all adverse effects of opioids, and improve analgesia. However, as it was seen in several our patients, while one pain could be better controlled with advent of naloxone, other pains became worse. Theoretically, this means that some of the pains were related to hyperalgesia and were sensitive to naloxone, while others could be even reversed or unmasked by the same dose of the drug. This may add to confusion,

but also explain why several clinicat trials lacking specificity yielded negative results. In most of our patients the dose of naloxone was titrated against constant dose of the opioid. Indeed the effective dose of naloxone was in reciprocal relationship to the dose of opioid, similar to the suggestion made by Crain and Shen [8]. This means that the tablets containing fixed ratio of oxycodone and naltrexone, may show in practice quite narrow pharmacologic window and the higher doses of these preparation may be ineffective.

Hypothetically, liver involved in pathological process may produce a number of abnormal endogenous opioids [27]. These opioids may modify pain sensation and provide endogenous analgesia (One of such cases was reported by one of us (ZZ) recently in another context [28]), pruritus [29] but also hyperalgesia. In several our patients liver was clearly involved in the malignant process and could be the source of opioids causing hyperalgesia. However, hyperalgesia responding to opioid antagonists was also observed in patients with diseases unrelated to liver pathology and suggest that OIH was induced only by the exogenous opioids. In this context exceptional is the last case of young woman with chronic, poorly defined pain in her leg, responding paradoxically to exogenous opioids. Dramatic response to naloxone and naltrexone, but without any exogenous opioid suggest that, indeed, the OIH was of endogenous origin. However, we do not have any information about the functioning of her liver, which could suffer of adipositas. It is thus possible that many pain conditions like in our patient remain undiagnosed and maltreated.

Ultra low opioid antagonists seems to be effective in the symptoms classified as opioid neurotoxicity. Especially important and valued by the patients is the effect of naloxone on delirium and agitation. Currently, using the same protocol of sc naloxone infusion, we treat many patients with terminal restlessness and agitation, allowing many patients to die without pain, peacefully with minimum of adverse effects of opioids.

However, naloxone infusion can also have potentially dangerous adverse effects. One of them is reversal of analgesia which is unpleasant but never dangerous. In one of our patients described above, naloxone infusion caused significant respiratory depression. This is consistent with the idea that respiratory depression of opioids is counteracted by the excitatory effect of opioids. This may explain why, respiratory depression is a problem only in the begin of therapy with opioids, but hardy ever causes problems later in the treatment. Inhibition of the excitatory effect of the opioids by naloxone leaves the patient with the inhibitory effect only. Since we observed this kind of respiratory depression, we included measurement of respiratory rate in our protocol. It is important to diagnose early this condition and discontinue naloxone. This drug has a very short half life time and depression ceases within minutes.

The bioavailability of naltrexone is approximately 5% in humans [30–32]. After absorption which is nearly complete drug is transformed in the liver to active metabolite 6-beta-naltrexol [30, 33]. In severe liver cirrhosis the bioavailability of naltrexone will increase while synthesis of the active metabolite will diminish [34]. The pharmacokinetics of the ultralow dose is unknown.

In the last years new data emerged suggesting that toll like receptors 4 (TLR4) localised in the spinal cord glia may be responsible for the phenomenon of opioid induced hyperalgesia [35–37]. These receptors can be activated in an astereospecific way by opioids [38]. Interestingly morphine-3- but not morphine-6-glucuronide are much more effective in stimulation of this receptors. This unravels a whole new world of possibilities. However, clinical proof of this concept is still lacking.

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