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Opioid – induced hyperalgesia after pancreas and kidney transplantation procedure – a case report

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Abstract

Background. Opioids are still the basic drugs in postoperative, moderate to severe pain treatment and also have been increasing in use for chronic pain patients. Common side effects of such therapies are usually well known. Opioid-induced hyperalgesia (OIH) is a rare phenomenon in opioid treatment. ***Case report.*** We present an original case of a 30-year-old female with OIH diagnosed in postoperative period after pancreas and kidney transplantation, reoperations and late post transplantation hospitalizations. This case suggests the possibility of OIH cross induction by different opioids. Multimodal approach to OIH treatment, including temporary propofol sedation in early postoperative period has been suggested to consideration. *Anestezjologia i Ratownictwo 2018; 12: 274-278*.

Keywords: opioid-induced hyperalgesia, transplantation procedure, fentanyl, propofol

Introduction

Opioids are fundamental drugs in acute and chronic pain and have been increasing in use for moderate to severe pain treatment. Despite of the analgesic potency, opioid treatment can cause side effects [1]. Opioids-based analgesia is frequently used in perioperative pain treatment model, so their potential side effects are usually well known in these settings. Unfortunately it is crucial for the practitioner to be aware not only of the common side. Opioid usage may paradoxally decrease pain thresholds, thus increase the response to a painful stimulation (hyperalgesia) and nonpainful stimuli (allodynia). Heightened pain sensitivity causes exacerbation of preexisting pain, despite increased opioid treatment and when other causes, such as painful disease progression were ruled out, the suspicion for the presence of OIH should be raised. Consciousness impairment, arousal, myoclonics and pain extension to other anatomic areas of distribution may also be observed [2]. In this study the importance of OIH diagnosis is highlighted. We present a case of severe, strong opioids untreatable, postoperative pain after organ transplantation, reoperations and late post transplantation hospitalizations.

Case report

A 30-year-old female was admitted to Transplantation Surgery Clinic for pancreas and kidney transplantation from deceased donor. 13 years history

of type 1 diabetes and chronic renal failure related to diabetic nephropathy, arterial hypertension, ventricular arrhythmia (treated with implanted cardioverter ICD-VVRI) were stated. She had chronic upper abdomen rushing and burning pain. No organic reason for this has been found. She was suspected of having superior mesenteric artery syndrome and treated with surgical duodeno-jejunalis flexure liberation and duodeno-jejunalis anastomosis, but it was ineffective for her pain status. Diabetic polyneuropathy was then suspected and successfully treated with transdermal buprenorphine system (up to 52.5 μg/h), amitriptyline (30 mg/day) and acupuncture. Two years before the transplantation her pain therapy was deescalated and finally withdraw. For a period of twenty months before the operation she had negative pain as well as pain treatment history. Her preoperation medication list included: bisoprolol 2.5 mg/day, pantoprazole 40 mg/day, calcium carbonate 3 g/day, alfa-lipoic acid 600 mg/day, insulin 28 IU/day.

The transplantation procedure was done. She was anesthetized with based on bispectral index monitoring target-controlled propofol infusion (2-3 μg/ml), intravenous fentanyl administration (0.003 mg/kg/h), cis-atracurium (4 mg/h). Immunosuppressive therapy included: tacrolimus 12 mg/day, mycophenolate mofetil 1 g/day and prednisone 7.5 mg/day. Postoperative pain was rated as 6-8 on Numeric Rating Scale (NRS; 0 = no pain, 10 = worst pain imaginable) in spite of increased continuous intravenous fentanyl infusion up to the dose used intraoperatively - 0.2 mg/h. She described her pain as sharp and burning sensation in the area of postoperative wounds with dull diffuse abdominal pain. Her blood pressure and pulse rate were also elevated [3]. In the 4th postoperative day pain was described by the patient as unbearable. Arousal, myoclonics and recurred essential consciousness impairment were observed. Due to ineffective fentanyl analgesia, sedation with continuous propofol intravenous infusion, tracheal intubation and mechanical ventilation were started. During that period no autonomic cardiovascular manifestation of acute pain were observed. Her blood pressure and pulse rate decreased. Before she was woken the thoracic epidural catheter had been inserted at Th 8-9 level. The postoperative pain was treated with continuous epidural analgesia with 0.1% bupivacaine and fentanyl (10 μg/ml). This management was also ineffective in her pain status and additionally pruritus appeared. For the above reasons the epidural infusion was discontinued and the catheter was removed after three days of treatment.

During the hospitalization the patient was reoperated three times. The duodeno-jejunal fistula repair, pancreas graftectomy with appendectomy and kidney graft revision with uretero-vesical anastomosis reconstruction were done. She was anesthetized with propofol (TCI) and *i.v.* fentanyl for all the cases. In each postoperative period she felt severe increased in time abdominal pain, treated with increasing amounts of fentanyl (0.1-0.15 mg/h), metamizol and paracetamol. Regularly at 72-96 hours after each surgical intervention critical abdominal pain aggravations (NRS 9-10) with coexisting psychical and motoric agitation and impaired logical contact were observed. To treat the first of them temporary opioid rotation from fentanyl to morphine was done, but also ineffectively for her pain status. During the second postoperative pain crisis, chronic pain physician diagnosed opioid-induced hyperalgesia. Fentanyl infusion was gradually discontinued and rotation to methadone in increased doses (up to 40 mg/day) was included. Additionally continuous lidocaine infusion (0.5 mg/kg/h) was administered. This treatment significantly reduced the postoperative pain level. During the third postoperative pain crisis, intravenously administered magnesium sulphate in a single dose of 2 g was unexpectedly effective (pain level reduction to NRS = 0 with in 24 hours). Amitriptyline treatment continuation and gabapentin administration in increased doses was included. She was discharged home with good pain control (NRS = 0) with oral medications (methadone 9 mg/day; amitriptyline 20 mg/day; gabapentin 900 mg/day). Oral magnesium supplementation was also recommended. Over this time her pain treatment was deescalated (in another center) and she reported being pain free.

Four months later she was admitted to the pain clinic (in our center) because of strong but episodic abdominal pain. She associated those episodes with urinary tract infections. Her actual pain treatment was reduced to amitriptyline 20 mg/day in monotherapy. Her magnesium serum level was normal. Sublingual buprenorphine (0.2-0.4 mg) in pain episodes was successfully included.

One year after her transplantation she was admitted to the hospital with rushing but diffuse dull abdominal pain with burning sensation (up to 10 in NRS) with coexisting psychical and motoric agitation and impaired logical contact. This state was

precluded by another painful urinary tract infection treated with *i.v.* tramadol (200 mg/day) in another center. Methadone titration (up to 25 mg po/day), buprenorphine 1.2 mg/day in regular dosage (6/day) and lidocaine continuous *i.v.* infusion (0.5 mg/kg/h) was started. Despite of normal magnesium serum level *i.v.* supplementation (2 g/day) was included. Sufficient analgesic (NRS = 0) and normal mental state was achieved after one day of treatment and it was then gradually deescalated to amitriptyline 20 mg/day and methadone 18 mg/day. She was discharged home in the 5th day of hospitalization.

Discussion

Escalated, up to effective, strong opioid dosages is still the basic model of moderate to severe pain treatment [4]. Unfortunately it can cause dose related pain aggravation – opioid-induced hyperalgesia (OIH). It is defined as enhanced pain response to a noxious stimulus, induced by opiate use. OIH increases sensitivity to existing painful condition by decreasing pain thresholds, whereby can aggravate a pain state. Therefore the differential diagnosis between OIH and progression in pain- inducing disease is crucial for including a proper treatment. Furthermore since Rossabach described anxiousness, sleep disorders, myoclonics and hyperalgesia as an OIH signs, it can be confused to opioid tolerance [2]. In fact they are different phenomena. In tolerance analgesic effect decreases in time with a constant opioid dosage and can be treated by increasing it. OIH related pain state cannot be improved with an increased opioid dose; furthermore this treatment can increase the pain sensation [5].

OIH is observed in perioperative analgesia and also in non-surgical painful settings [5].

Importantly, a meta-analysis demonstrated that while OIH can be consistently present in patients given remifentanil, its occurrence after acute fentanyl exposure is limited and conflicting [6]. Up to January 2015 six randomized, controlled trials evaluating the effect of fentanyl on pain in the acute setting have been conducted. Two trials oppose whereas four trials support the occurrence of fentanyl-induced hyperalgesia [6].

Presented case demonstrates the possibility of OIH after perioperative intravenous fentanyl analgesia, and stays in line with recent Mauermann study on healthy volunteers [7].

Tramadol as an OIH inducer was described in only one case report in human [8]. The present raptor supports the possibility of tramadol inducted OIH since this treatment aggravated abdominal pain due to painful urinary tract inflammation. This can also suggests the possibility of OIH cross induction by different opioids (fentanyl and tramadol). Such phenomenon has not been described in literature yet.

To date, reduction of opioid doses administered (up to 25-30% every 48-72 h) in step with including and escalation of antyhyperalgesic acting opioids, partial mi opioids receptors agonist – buprenorphine or methadone dosage is the postulated pharmacologic regiments for OIH treatment [9]. Methadone is also an NMDA antagonist. As well as another antagonist – ketamine it has been used in OIH prevention and treatment [9]. Intravenous administration NMDA inhibitor – magnesiumsulphate can be effective in OIH prevention, despite of normal magnesium serum level [10]. Another postulated treatments are gabapentin and pregabalin [11,12]. Systemic lidocaine administration was also effective in remifentanil inducted OIH inhibition in rats [13]. Continuous *i.v.* infusion of propofol – type-A γ-aminobutyric acid receptor (GABA A) antagonist is also postulated to be effective in OIH treatment [14] probably *via* N-Methyl-D-Aspartate (NMDA) receptors and endocannabinoid system modulation [15,16]. Regional analgesia (RA) compared to systemic analgesia is beneficial in better postoperative pain control [17]. However RA is suspected to be ineffective in OIH treatment, especially when high dosage of systemic opioids or intrathecal morphine is administered despite a sensory lost in the operated area [18,19].

In present case ineffectiveness of epidural analgesia (EA) could be explained with previous systemic administration of fentanyl in increased - up to high doses. This opioid agent has also been added as an adjuvant to epidurally administered bupivacaine. Because of its potential rostral ventromedial medulla area of action in this setting, fentanyl could potentially become an OIH sustained factor and was likely the reason of limited EA with bupivacaine in this case.

In case we described the patient was treated effectively with methadone and buprenorphine. Continuous lidocaine infusion, intravenous magnesium sulfate and gabapentin were also effectively used. We continued amitripiline treatment because it modulates serotoninergic and noradrenergic antinociceptive pathways and it is recommended as a first line treatment of neuropathic pain [20]. Complete pain relief during propofol

sedation could be the effect of its impact on NMDA receptors and endocannabinoid system, causing a brake in the OIH positive retro-feeding mechanism. Interestingly its antyhyperalgesic effect continued over the ineffective EA and stops immediately after propofol infusion discontinuation. This fact suggests the possible propofol impact on OIH.

Conclusion

Opioid rotation is a wildly postulated procedure in OIH treatment [5]. In case we described multimodal pharmacotherapy approach was effective in each OIH pain aggravation. Because of a critical postoperative pain level in OIH suspected patients as well as postulated propofol antyhiperalgesic properties, sedation with this agent should be taken into consideration to temporary OIH management while opioid rotation or other additional treatment options are conducted [14-16].

Konflikt interesów / Conflict of interest
Brak/None

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