Can J Anesth/J Can Anesth (2014) 61:826–831
DOI 10.1007/s12630-014-0193-y

CASE REPORTS / CASE SERIES

Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone® for chronic pain: a case report

Gestion périopératoire d'un patient subissant la fermeture d'une fenêtre de Clagett stabilisé par Suboxone® pour douleur chronique: une étude de cas

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Received: 29 March 2014 / Accepted: 10 June 2014 / Published online: 2 July 2014

Abstract

Purpose *Buprenorphine is a semisynthetic opioid with both agonist and antagonist activity at the opioid receptor. Currently, buprenorphine is commonly available in sublingual preparations combined with naloxone (e.g., Suboxone®, Subutex®). There has been increased use of buprenorphine derivatives in the areas of substance addiction and chronic pain. Nevertheless, there is limited and conflicting information in the literature pertaining to the optimal management of buprenorphine-stabilized patients presenting for surgery. We present our experience with a chronic pain patient on buprenorphine presenting for thoracic surgery.*

Clinical features *A 47-yr-old female with a history of a Clagett window procedure for pulmonary aspergillosis and subsequent chronic pain presented to our institute for a window closure procedure. Preoperatively, her pain regimen included Suboxone 16 mg bid, which was continued perioperatively. Postoperatively, her course was complicated by suboptimal pain at the surgical site requiring in excess of 70 mg/24 hr of intravenous hydromorphone. Liberal addition of long-acting oral opioids was ineffective in improving pain management. Eventually, concern was raised regarding opioid receptor blockade by her long-acting Suboxone, and the decision was made to taper her Suboxone. Following this, her pain control improved dramatically and her opioid requirements were markedly reduced. By discharge, her Suboxone was discontinued and she was managed on oral hydromorphone.*

Conclusion *In a chronic pain patient continued on Suboxone perioperatively, significant improvement in control of postoperative pain was observed following tapered doses, and eventually her use of Suboxone was discontinued. This case highlights the potential for opioid receptor blockade by Suboxone, which can interfere with acute pain management.*

Author contributions *Alexander Huang* was involved in drafting the manuscript. *Alexander Huang, Rita Katznelson, Marc de Perrot,* and *Hance Clarke* contributed to manuscript revision.

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Résumé

Objectif *la buprénorphine est un opioïde semisynthétique ayant à la fois une activité agoniste et antagoniste sur les récepteurs des opiacés. Actuellement, la buprénorphine est facilement disponible en préparations sublinguales combinée à la naloxone (par exemple: Suboxone®, Subutex®). Il y a eu une augmentation croissante des dérivés de la buprénorphine dans les domaines de la toxicomanie et de la douleur chronique. Il existe néanmoins dans la littérature une information limitée et contradictoire sur la gestion optimale des patients stabilisés par la buprénorphine et se présentant*

pour une intervention chirurgicale. Nous présentons notre expérience d'une patiente souffrant de douleurs chroniques et recevant de la buprénorphine qui s'est présentée pour subir une chirurgie thoracique.

Caractéristiques cliniques *Une femme âgée de 47 ans ayant un antécédent d'intervention pour fenêtre de Clagett pour aspergillose pulmonaire et douleur chronique subséquente s'est présentée dans notre institut pour une procédure de fermeture de la fenêtre. Son traitement préopératoire pour la douleur incluait Suboxone 16 mg, deux fois par jour, qui a été poursuivi en peropératoire. En postopératoire, son évolution a été compliquée par une douleur sous-optimale au niveau du site chirurgical nécessitant plus de 70 mg/24 h d'hydromorphone intraveineuse. Un ajout généreux d'opioïdes à longue durée d'action par voie orale n'est pas parvenu à améliorer la gestion de la douleur. Éventuellement, un questionnement sur le blocage des récepteurs opiacés par le Suboxone à longue durée d'action a été soulevé et la décision a été prise de réduire sa dose de Suboxone. À la suite de cette réduction, le contrôle de la douleur a été considérablement amélioré et les besoins en opioïdes ont diminué de façon marquée. À son congé de l'hôpital, le Suboxone a été arrêté et la douleur a été contrôlée avec de l'hydromorphone par voie orale.*

Conclusion *Chez une patiente souffrant de douleur chronique traitée de façon continue par Suboxone en périopératoire, une amélioration significative du contrôle de la douleur postopératoire a été observée après la réduction des doses de Suboxone, jusqu'à l'arrêt définitif de son utilisation. Ce cas illustre la possibilité de blocage des récepteurs opioïdes par la Suboxone, pouvant interférer avec la gestion de la douleur aiguë.*

Buprenorphine is a semisynthetic opioid with agonist and antagonist effects at the opioid receptor. Initially introduced in the 1980s as an analgesic, the past few decades have seen buprenorphine evolve to have roles in the realms of chronic pain and substance addiction.[1,2]

While well investigated in chronic pain and substance addiction, there is a paucity of data, as well as lack of consensus in the literature regarding management of patients using buprenorphine (and its derivatives) in the perioperative setting. In this case report, a patient using Suboxone® for chronic pain underwent a Clagett window closure at our institution and presented a considerable challenge in terms of postoperative pain management. We describe our involvement with the perioperative management of buprenorphine with the hope that others may benefit from our experience.

Case

Written informed consent was obtained from the patient for publication of this report. A 47-yr-old female (weight, 48 kg) with a history of chronic pain presented to our institution for a Clagett window closure procedure. This was in the context of a bronchopleural fistula following right upper lobectomy for pulmonary aspergillosis. Her management was further complicated by nociceptive and neuropathic pain in both her chest and right arm which has persisted for several months. Several strategies and therapies were attempted to alleviate her pain, including oxycodone up to 260 mg, fentanyl patch 100 $\mu g \cdot hr^{-1}$, Cymbalta®, cyclobenzaprine, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and a transcutaneous electrical nerve stimulation unit. These were all discontinued or abandoned due to lack of benefit or side effects. The nature of our patient's pain consisted primarily of chest wall pain at the site of her Clagett window, which was burning and aching in quality and often radiated to her right shoulder and jaw. On physical exam, her chest wall pain was reproducible on palpation of the Clagett window site, but there was no notable skin edema, hyperalgesia, or allodynia. Her baseline level of pain at the time of surgery was 7/10 on a numeric rating scale (NRS), but she often experienced episodes of 10/10 pain. Her functional status had deteriorated considerably due to her pain, and she required assistance with several activities of daily living. At the time of her surgery, her pain regimen included Suboxone 16 mg *bid*, gabapentin 1,200 mg *tid*, venlafaxine 225 mg *od*, and nabilone 1 mg *bid.*

On the day of her surgery, she underwent a general anesthetic with endotracheal intubation. A thoracic epidural was placed preoperatively at the T6 level. Intraoperatively, she received a total of ketamine 45 mg *iv* and hydromorphone 1.6 mg *iv*. The ketamine was administered at induction (25 mg) and as intermittent boluses (total 20 mg) during the case. The procedure took approximately 2.5 hr. Tracheal extubation was performed in the operating room and our patient was brought to the postanesthetic care unit without issue. The Acute Pain Service was consulted for postoperative pain management.

Our patient's usual analgesic regimen was resumed on postoperative day (POD) 1. She received 0.2% ropivacaine 5 $mL \cdot hr^{-1}$ via her thoracic epidural and hydromorphone intravenous patient-controlled analgesia (IVPCA) with a bolus dose of 0.6-0.8 mg every five minutes and a four-hour limit of 16 mg. Immediately postoperatively, surgical site pain was well controlled with the thoracic epidural; however, she developed new right shoulder pain with radiation to her right hand and numbness to her digits. The Neurology Consultation Service assessed her for a possible

right brachial plexus injury, and on examination, she was found to have reduced range of motion in all axes of the shoulder and mild weakness of all upper extremity muscle groups. Nerve conduction studies were normal, and results of an electromyogram showed findings consistent with a stretch injury. It was thought that her new right upper extremity symptoms were secondary to a brachial plexus stretch injury from intraoperative positioning.

By POD 5, the thoracic epidural began to fail, resulting in increased pain at the surgical site requiring hydromorphone IVPCA 15-20 mg/24 hr. This pain was sharp and burning in quality and 7-8/10 on the NRS, often reaching 10/10. The thoracic epidural was removed on POD 7. Following the removal of the epidural, her pain became increasingly difficult to manage, requiring hydromorphone IVPCA 30-40 mg/24 hr. Of note, she continued to receive her usual home analgesics during this period, including her Suboxone.

In addition to IVPCA, Hydromorph Contin® 12 mg *bid* was added on POD 11 for improved background analgesia, and the dosage was increased to 24 mg *bid* soon after, with little benefit. During this period, her hydromorphone PCA requirements increased to 50-70 mg/24 hr for nearly persistent 10/10 pain. At this point, the Acute Pain Service questioned the possibility of analgesic interference by Suboxone. The Hydromorph Contin was discontinued, and our patient's Suboxone dose was tapered to 16 mg *od* (as opposed to *bid*). Immediately following this 50% decrease in her Suboxone dose, her pain control markedly improved. Her NRS scores were consistently 7-8/10 in the first days following the taper, and her IVPCA requirements decreased to 15-25 mg/24 hr. Within ten days of reducing her Suboxone, the IVPCA was discontinued, and she was transitioned to oral hydromorphone. Her Suboxone was further reduced at this point to 8 mg *od*.

Our patient was finally discharged on POD 41. Her discharge was delayed in part by her surgical site pain but also by persistent chest tube air leaks as well as workup and management of her brachial plexus injury with physiotherapy. At the time of discharge, her Suboxone had been discontinued completely, and her analgesic regimen consisted of Hydromorph Contin 9 mg *tid*, baclofen 10 mg *tid*, gabapentin 1,200 mg *tid*, venlafaxine 225 mg *od*, and nabilone 1 mg *bid*. The range of her pain scores on discharge was 3-5/10, which was lower than her preoperative baseline.

Our patient was seen in follow-up three weeks post-discharge (approximately two months postoperatively), at which point her surgical site pain ranged from 3-7/10 on the discharge analgesic regimen. There was notable improvement in her right shoulder range of motion and normal power in her right upper extremity. She continued to experience residual numbness in her fingers. When offered to transition back to Suboxone, she declined citing both satisfaction with her current pain regimen and dissatisfaction with Suboxone due to nausea and anorexia associated with its use. Consequently, she was continued on Hydromorph Contin with the goal to titrate down over the following months. Her surgical site pain and brachial plexus injury continued to improve six months postoperatively, allowing for further tapering and discontinuation of her analgesics. During her follow-up visits, she confirmed that her pain was considerably improved from her preoperative status despite the extensive pain management challenges she endured (the Table summarizes the patient's postoperative therapy).

Discussion

This case report highlights the considerable challenges that anesthesiologists and surgeons face when managing postoperative pain in patients with chronic pain stabilized on buprenorphine. Given the increasing trend for using buprenorphine in the management of both chronic pain and opioid dependence, strategies are needed for the management of acute pain in these patients.

Buprenorphine's pharmacologic and analgesic effects are mediated through its partial μ-opioid agonist and κ-opioid antagonist activity.[1] Buprenorphine is recognized for having a high binding affinity but relatively low intrinsic activity for the opioid receptor, making it ideal in the management of opioid dependence. In addition to its direct analgesic effect, buprenorphine has been shown to reduce central pain sensitization and hyperalgesia,[3,4] furthering its value in chronic pain management. Furthermore, through κ-opioid receptor antagonism, buprenorphine is considered by some to produce antidepressant and mood stabilizing effects; however, this remains subject to some debate.[5]

Though available in parenteral and transdermal preparations, buprenorphine is most commonly administered through sublingual forms. The analgesic effect of buprenorphine occurs at dose ranges from 0.1-7 mg,[6] depending on mode of administration.[7] Sublingual buprenorphine doses can reach as high as 32 mg·day^{-1} in divided doses. Beyond 32 mg·day^{-1}, a ceiling effect in terms of analgesia occurs due to the partial agonist effect of buprenorphine at the opioid receptor.[7] Relative to morphine, the potency of buprenorphine is 30-40-fold greater.[8] Sublingual preparations of buprenorphine are well absorbed, with a bioavailability of 60-70%.[9] The sublingual form has a half-life of 24-60 hr, and occupancy at the opioid receptor can last up to five days.[10] Metabolism of buprenorphine occurs through CYP

Table Summary of the patient's postoperative analgesic therapies

POD	Pain (NRS) (/10)	Analgesic therapy
Preoperative	7-10	Suboxone® 16 mg *bid*, adjuvants
1-4	< 5	TEA[1] Ropivacaine 0.2% (5 mL·hr^{-1}), Hydromorphone PCA (5-10 mg/24 hr), Suboxone 16 mg *bid*, adjuvants
5-7[2]	7-10	TEA[1] Ropivacaine 0.2% (5 mL·hr^{-1}), *Hydromorphone PCA (15-20 mg/24 hr)*, Suboxone 16 mg *bid*, adjuvants, *baclofen 5 mg tid.*
8-10	10	*Hydromorphone PCA (30-40 mg/24 hr)*, Suboxone 16 mg *bid*, adjuvants *baclofen 10 mg tid.*
11	10	*Hydromorphone PCA (50 mg/24 hr), Hydromorph Contin® 12 mg bid*, Suboxone 16 mg *bid*, adjuvants baclofen 10 mg *tid*.
12	10	*Hydromorphone PCA (70 mg/24 hr), Hydromorph Contin 24 mg bid*, Suboxone 16 mg *bid*, adjuvants baclofen 10 mg *tid*.
15	10	*Hydromorphone PCA (70 mg/24 hr), Hydromorphone Contin 24 mg bid*, Suboxone 16 mg *bid*, adjuvants, baclofen 10 mg *tid*.
16-25	7-8	*Hydromorphone PCA (15-25 mg/24 hr), Suboxone 16 mg od*, adjuvants, baclofen 10 mg *tid*.
26-30	7	*Suboxone 8 mg od*, *Hydromorphone 4 mg q2 h prn (36 mg/24 hr),* adjuvants, baclofen 10 mg *tid.*
31-35	5-7	*Suboxone 4 mg od*, *Hydromorphone 4 mg q2 h prn (32 mg/24 hr),* adjuvants, baclofen 10 mg *tid.*
36-41[3]	3-5	*Hydromorph Contin 9 mg tid,* adjuvants baclofen 10 mg *tid*.
2 Months	5-7	
4 Months	< 5	*Hydromorph Contin 9/6/9 mg tid,* gabapentin 1,200 mg *tid* venlafaxine 225 mg *od*.
6 Months	< 4	*Hydromorph Contin 9/6/9 mg tid,* gabapentin 800 mg *tid,* venlafaxine 225 mg *od*

Major changes denoted in italics

[1] Thoracic epidural analgesia

[2] Epidural removed POD 7 for failure

[3] Discharged POD 41

Adjuvants include gabapentin 1,200 mg *tid*, venlafaxine 225 mg *od*, nabilone 1 mg *bid*

NRS = numeric rating scale; PCA = patient-controlled analgesia; POD = postoperative day

3A4, resulting in inactive metabolites, with the exception of nor-buprenorphine which has respiratory depressant effects.

Buprenorphine-naloxone preparations (i.e., Suboxone, Subutex) were introduced in the 2000s in response to the growing use of buprenorphine in the management of opioid addiction.[2] Naloxone, a high affinity μ-opioid antagonist, has poor oral bioavailability but can induce withdrawal symptoms if administered parenterally, discouraging misuse or diversion of Suboxone and Subutex. Suboxone, the focus of this case report, is a buprenorphine-naloxone preparation available as a sublingual film, where the buprenorphine:naloxone ratio is 2 mg:0.5 mg (available in formats of 2 mg:0.5 mg, 4 mg:1 mg, 8 mg:2 mg, and 12 mg:3 mg).

In the case of our patient, she experienced severe postoperative pain despite receiving both her usual analgesic regimen and large amounts of intravenous and oral opioids. The refractory nature of her pain was likely due to the saturation of opioid receptors by buprenorphine, which limited the effect of additional opioids administered.[11,12] The occupation of receptors by buprenorphine can last for several days.[10] Our patient was receiving the maximum recommended dose of Suboxone (32 mg·day^{-1}), which accounts for it to appear to produce complete occupancy of her opioid receptors and explains the lack of effectiveness of hydromorphone IVPCA and long-acting oral opioid preparations for pain control after her epidural was discontinued. Furthermore, receptor affinity of buprenorphine is sufficiently strong enough to displace other recently administered opioid agonists from the opioid receptor.[13] Soon after reducing the Suboxone dose, her pain control improved considerably, reflecting the binding of the full opioid agonists to the newly available receptors.

There are limited recommendations in the literature regarding the optimal perioperative management of buprenorphine-stabilized patients. A small number of case reports are available describing varying experiences with buprenorphine management before surgery; however, none involve patients undergoing thoracic surgery. Reviews on the topic recommend continuation of buprenorphine through the perioperative period, favouring this approach over discontinuation before surgery wherever possible.[13-15] As their rationale for continuation, the authors in these reviews cite the risk of buprenorphine withdrawal as well as the ability to use

higher doses of full-opioid agonists to manage pain successfully. This has been clearly shown in case reports involving obstetrical patients.[16,17] More recently, a case series was published describing the successful maintenance of stable doses of buprenorphine in patients undergoing major surgery.[2] In the seven cases presented, postoperative pain was managed through increased buprenorphine dosing and/or introduction of full opioid agonists. Some authors have recommended increasing the current dose of buprenorphine by 25% of a patient's baseline dose.[13] Conversely, one published guideline suggests reducing the buprenorphine dose to 8 mg preoperatively in patients requiring 10 mg or more of the drug and supplementing the remainder of the buprenorphine dose with short-acting full-opioid agonists.[18]

Our experience suggests that the buprenorphine-induced opioid receptor blockade is not easily overcome through administration of high doses of full opioid agonists. This has been observed in published case reports as well[19] and has led some to recommend that buprenorphine should be discontinued three to seven days preoperatively and that patients should be converted to a full agonist to avoid receptor blockade.[20,21] Published protocols also suggest discontinuation of buprenorphine preoperatively for painful procedures.[22] A potential pitfall of this strategy is that subsequent reintroduction of buprenorphine postoperatively and post-discharge requires discontinuation of the full-opioid agonists, which risks both pain and withdrawal. The difficulty in our patient's pain management may partly stem from her relatively high analgesic requirements preoperatively, which differs from previously described case reports. There may also be a dose in which a patient such as ours was saturated at her opioid receptor sites, and the ability to increase buprenorphine and gain a therapeutic effect is limited. Given that she was already receiving the maximum recommended dose of Suboxone, we did not attempt to increase the dose as a strategy to improve pain control.

The naloxone content in her Suboxone dose may also have been a factor in her poorly controlled pain. As previously mentioned, the naloxone present in Suboxone has limited clinical effect when administered sublingually, and it serves primarily as a mechanism to deter intravenous injection. Nevertheless, 32 $mg \cdot day^{-1}$ of Suboxone includes 8 mg of naloxone absorbed sublingually, which is an appreciable dose. Sublingual naloxone doses $\geq$ 4 mg have been shown to precipitate withdrawal symptoms in opioid-dependent patients.[23] This suggests that higher doses of sublingual naloxone can produce antagonist effects at the opioid receptor. Thus, in addition to the buprenorphine-associated receptor blockade, the amount of naloxone absorbed may also contribute to the ineffectiveness of intravenous hydromorphone exhibited in this case.

This case may imply that opioid receptor blockade may be significant and refractory to full opioid agonists in patients with chronic pain requiring higher doses of Suboxone (and buprenorphine alone). In this population, perioperative management may require the conversion to a full agonist before surgery; however, there is a lack of evidence relating to this issue in the literature.

The aim of this case report is to highlight the lack of a consensus on the perioperative management of patients presenting on Suboxone treatment and to provide information that may help perioperative physicians manage this potentially complex clinical situation. More research and discussion is required in order to provide clear and definitive guidelines for the optimal perioperative management of buprenorphine-stabilized patients.

Conflicts of interest None declared.

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