



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Case Report

Intravenous Buprenorphine Micro-dosing Induction in a Patient on Methadone Treatment: A Case Report

Kelly Crane, M.D., Jessica Snead, Pharm.D., B.C.G.P., B.C.P.S.,
Robert Stanley, M.D., Ph.D., Jonathan Avery, M.D.,
Sumantra Monty Ghosh, B.Sc., M.B.T., M.Sc., M.D., F.R.C.P.C., D.M.-E.M.D.M.,
I.S.A.M.(C.), C.S.A.M., Gregory Mints, M.D., F.A.C.P.

Introduction

Methadone used in the treatment of opioid use disorder (OUD) can exacerbate respiratory insufficiency in patients with pulmonary and breathing disorders, such as chronic obstructive pulmonary disease (COPD) and obesity-hypoventilation syndrome. There are several options available to patients on methadone who are hospitalized for respiratory failure. The methadone dose can be decreased to avoid respiratory depression, patients can be detoxed off methadone completely, or, while still hospitalized, an alternative maintenance medication, such as long-acting injectable naltrexone or buprenorphine, can be initiated. Inpatient initiation of buprenorphine has been shown to result in better long-term treatment adherence and less illicit opioid use 6 months after hospitalization than detoxification.¹ In addition, previous studies have demonstrated improved opioid relapse-free survival with buprenorphine maintenance compared with long-acting injectable naltrexone.²

Buprenorphine is a partial μ -opioid receptor agonist with high receptor-binding affinity³ and a limited potential to cause respiratory depression.⁴ Initiation of buprenorphine is often fraught with concerns about precipitated withdrawal as well as the prolonged time period required for successful and safe transition. Standard buprenorphine induction requires patients to go through an initial period of moderate opioid withdrawal.⁵ Opioid withdrawal is unpleasant, unacceptable to many patients, and may decrease patient acceptance

of the medication. Failure to wait long enough before buprenorphine induction typically leads to severe precipitated opioid withdrawal, which can be associated with agitation and delirium.⁶ Increased duration of hospitalization is also frequently a concern because of cost and increased risk of patients leaving against medical advice, before the induction is completed. Thus, despite the impetus to starting maintenance treatment during hospitalization,¹ implementation of inpatient buprenorphine induction protocols remains challenging. Because of methadone's long half-life, the aforementioned challenges are particularly prominent with transition from methadone to buprenorphine.

Unlike traditional induction, buprenorphine micro-dosing allows for initiation of buprenorphine without requiring a period of opioid withdrawal. Successful protocols using sublingual (SL)⁷⁻¹⁰ and transdermal¹¹ forms have been reported. Micro-dosing is intended to both improve tolerability and decrease duration of induction.

Received June 9, 2020; revised July 16, 2020; accepted July 17, 2020. From the Department of Medicine (K.C., R.S., G.M.), Weill Cornell Medical College, New York, NY; Department of Pharmacy (J.S.), New York-Presbyterian Hospital, New York, NY; Department of Psychiatry (J.A.), Weill Cornell Medical College, New York, NY; Department of General Internal Medicine and Neurology (S.M.G.), University of Alberta, Alberta, Canada; Department of Medicine and Psychiatry (S.M.G.), University of Calgary, Alberta, Canada. Send correspondence and reprint requests to Gregory Mints, M.D., F.A.C.P., 525 East 68th Street, Starr Building 517, New York, NY 10065; e-mail: Grm9032@med.cornell.edu

© 2020 Academy of Consultation-Liaison Psychiatry. Published by Elsevier Inc. All rights reserved.

Case Report

Usual starting micro-doses of buprenorphine are 0.3–0.5 mg or 15–25% of the initial SL doses of the standard induction. Such low doses of buprenorphine are not available in SL formulation in the United States. The manufacture package insert instructs not to divide the tablets,¹² and although the practice certainly exists,¹³ local pharmacy policies vary among hospitals. The buprenorphine transdermal patch is available in small dosages, but it is not available in a generic form and is expensive.¹⁴ In comparison, generic intravenous buprenorphine, which is usually used for pain management,¹⁵ is readily available and is inexpensive.¹⁴

We report a case of a patient successfully transitioned from methadone to buprenorphine during hospitalization using a novel intravenous buprenorphine micro-dosing protocol.

Case Vignette

A 62-year-old man, Mr. A, on chronic methadone 80 mg daily for OUD presented to his primary care provider feeling unwell. He was found to be lethargic, with an arterial oxygen saturation by pulse oximeter of 74% on room air, which improved to 96% with supplemental oxygen. He was referred to the emergency department of our hospital. On arrival to the emergency department, he was altered, had a respiratory rate of 6 per minute, and pin-point pupils. IV naloxone 0.4 mg was administered x2 with improvement in his mental status and respiratory rate, confirming the diagnosis of opioid overdose. He was then (at 8 pm on hospital day [HD] 1) started on continuous naloxone infusion at 0.06 mg/h. Methadone was held. Admission venous blood gas analysis is shown in Table 1. Urine toxicology screen was positive for methadone and cannabis only. Blood ethanol level was undetectable. Liver and renal function were normal. He was admitted to the medicine service step down unit, where he remained until discharge.

Mr. A had a history of obesity (on admission weight 101 kg, body mass index 26.5 kg/m²) and COPD. He used intranasal heroin intermittently for 20+ years. One year before, Mr. A was admitted to the hospital with respiratory failure because of heroin overdose. He was since maintained on 80 mg of methadone daily in his outpatient treatment program. He could not specify when his last heroin use was but stated that it was not recent. He denied taking more

TABLE 1. Venous Blood Gas Analysis

Time	pH	pCO ₂	pO ₂	Bicarb	O ₂ sat	FiO ₂
Admission	7.29	92	23	44	33%	RA
HD 3, on Naloxone	7.39	67	39	41	73%	3L NC
Discharge	7.44	57	60	39	92%	3L NC

Bicarb = bicarbonate concentration; FiO₂ = partial pressure of inspired oxygen; HD = hospital day; NC = nasal canula; pCO₂ = partial pressure of carbon dioxide; pO₂ = partial pressure of oxygen; O₂ sat = oxygen saturation; RA = room air.

methadone than prescribed. He reported one attempt at buprenorphine treatment 3 years before and underwent induction at home. However, he stopped taking the medication soon thereafter when he relapsed on heroin. He lived alone in the New York City borough of the Bronx and was receiving disability benefits.

Mr. A verbally consented to transition off methadone. Education about buprenorphine was provided. Mr. A expressed his strong preference to avoid withdrawal symptoms as much as possible. He was then offered a micro-dosing induction protocol with intravenous buprenorphine and was informed that this would be an off-label use of an otherwise Food and Drug Administration–approved medication. Potential side effects were reviewed, and Mr. A gave his verbal consent to proceed. Before discharge, Mr. A was asked for permission to submit this case report for publication, which he gave in writing.

IV buprenorphine was supplied in single use 1-ml vials of 0.3 mg/ml buprenorphine. The dosing was based on reported bioavailability of the SL form of 30–50%.^{16,17} Q6h dosing schedule of IV buprenorphine dosing was chosen based on reported half-life of up to 8.6 h (after a single dose of <1 mg)¹⁸ and the standard recommendation of Q6-8h dosing for pain management. Buprenorphine was administered IV via a peripheral venous catheter as a rapid push.

Although very rapid buprenorphine induction (8h) of a patient on 50 mg of methadone daily has been reported,¹⁹ we chose a conservative 4-day induction schedule similar to previously reported SL protocols.⁸

The induction protocol and clinical course are summarized in Table 2.

The naloxone infusion was discontinued at 11 am on HD 3. Methadone was restarted at 25 mg Q12h at 5 pm on HD 3. The IV buprenorphine micro-dosing

TABLE 2. Induction Protocol and Clinical Course

Induction day	Time	Current dose, mg				Cumulative dose over preceding 24h, mg			Events	
		IV	Vials	SL equivalent, low	SL equivalent, high	IV	SL equivalent, low	SL equivalent, high		
IV BUP Q6h, continue methadone 25 Q12h (5 am and 5 pm)										
1	6 pm	0.1	1	0.2	0.33	0.1	0.2	0.3	COWS = 0	
2	12 mn	0.2	1	0.4	0.67	0.3	0.6	1.0	COWS = 0	
	6 am	0.3	1	0.6	1	0.6	1.2	2.0	COWS = 0	
	12 noon	0.3	1	0.6	1	0.9	1.8	3.0	COWS = 10.	
									Started:	
									• IV fluids	
									• Ondansetron 8 mg IV × 1	
									• Clonidine 0.1 mg PO Q8h standing	
3	6 pm	0.3	1	0.6	1	1.1	2.2	3.7	COWS = 0–3	
	12 mn	0.3	1	0.6	1	1.2	2.4	4.0	COWS = 0–3	
	6 am	0.3	1	0.6	1	1.2	2.4	4.0	Ondansetron 8 mg IV × 1–20 min after BUP dose	
	12 noon	0.3	1	0.6	1	1.2	2.4	4.0	COWS = 0–3	
									COWS = 0–3	
	6 pm	0.3	1	0.6	1	1.2	2.4	4.0	Ondansetron 8 mg IV × 1–4.5h after BUP dose	
	12 mn	0.4	2	0.8	1.33	1.3	2.6	4.3	COWS = 0–3	
	6 am	0.4	2	0.8	1.33	1.4	2.8	4.7	COWS = 0–3	
	12 noon	0.4	2	0.8	1.33	1.5	3.0	5.0	COWS = 0–3	
	6 pm	0.4	2	0.8	1.33	1.6	3.2	5.3	COWS = 0–3	
4	12 mn	0.5	2	1	1.67	1.7	3.4	5.7	COWS = 0–2	
	6 am	0.5	2	1	1.67	1.8	3.6	6.0	Clonidine discontinued	
	12 noon	0.5	2	1	1.67	1.9	3.8	6.3	COWS = 0–2	
									COWS = 0	
Switch to SL BUP Q2h, d/c methadone										
	6 pm			2			5	7.0	COWS = 0	
	8 pm			2			7	9.0	COWS = 0	
	10 pm			2			9	11.0	COWS = 0	
	12 mn			4			12	13.3	COWS = 0	
5	6 am			6			17	17.67	COWS = 0	
d/c home with Rx for BUP/Naloxone SL 16/4 QD to start on day 6 am										
Total vials used			23							

BUP = buprenorphine; COWS = Clinical Opiate Withdrawal Scale; IV = intravenous; SL = sublingual.

Case Report

induction protocol was initiated at 6 pm on HD 3 (induction day 1) [Table 2](#).

Except for a single short episode, Mr. A demonstrated very few, if any, signs or symptoms of opioid withdrawal (Clinical Opiate Withdrawal Scale [COWS] 0–3) throughout his admission. On HD 4 (induction day 2), 2 hours after the administration of the second dose of 0.3 mg buprenorphine, sweating, nausea, and yawning were reported. His COWS score was 10. IV fluids, ondansetron 8 mg IV every 8 hours as needed, and clonidine 0.1 mg orally every 8 hours standing were administered with immediate resolution of his symptoms. He required a total of 3 doses of 8 mg IV ondansetron between HD 4 and HD 5. Mr. A remained well until discharge (COWS 0–2). Clonidine was discontinued because of borderline low blood pressure on HD 6 (induction day 4). On HD 7 (induction day 5), Mr. A was transitioned to SL buprenorphine dosed every 2 hours until the total dose within the preceding 24h reached 16 mg. This titration scheme was based on our previous experience, as well as others.²⁰ He was discharged on HD 8 with a prescription for buprenorphine/naloxone SL film 16 mg/4 mg daily and an appointment with his outpatient treatment program, which also provided buprenorphine treatment. Mr. A was also prescribed 2L oxygen per NC on discharge and given an outpatient pulmonology referral with the working diagnosis of obesity-hypoventilation syndrome.

At 4 weeks after discharge, Mr. A had a telephone follow-up. He reported feeling well and denied any methadone or illicit opioid use since discharge, or any opioid cravings. Per Mr. A, he was taking buprenorphine/naloxone as prescribed. However, he had been unable to connect to the outpatient buprenorphine provider, presumably because of the disruptions caused by the COVID-19 pandemic. At that time, his buprenorphine prescription was renewed, and additional steps were taken to ensure transition to an outpatient provider.

Discussion

We report a case of patient with COPD, and likely obesity-hypoventilation syndrome on methadone who was admitted with a second episode of acute respiratory failure. After initial treatment with continuous IV

naloxone infusion, Mr. A underwent successful inpatient IV buprenorphine micro-dosing induction. The induction was performed without interruption of methadone treatment or precipitation of significant opioid withdrawal. To the best of our knowledge, this is the first report describing micro-induction with IV buprenorphine.

An often-cited concern regarding IV administration of buprenorphine is a potential to cause euphoria or a “high”. Indeed, IV buprenorphine caused euphoria in healthy adults not on opioids²¹ and in patients with OUD who completed inpatient detox.²² SL buprenorphine is routinely diverted to be crushed and injected IV²³ because it can cause a high. It should be noted, however, that because SL bioavailability of buprenorphine is 30–50%,^{16,17} such injection would result in drug blood levels 2–3 times higher than intended. In addition, SL doses of the drug used for OUD maintenance are 2 orders of magnitude higher than those used for pain control.¹⁵ We are unaware of any reports suggesting that analgesic (0.1–1 mg) doses of intravenous buprenorphine would cause euphoria in patients already on high doses of opioids, including methadone. We therefore considered this approach safe. Notably, Mr. A specifically reported (and was surprised by) lack of any euphoric effect of the medication.

During the induction, Mr. A had a single episode of mild opioid withdrawal, which was brief and easily managed. The symptoms occurred only once the 24-hour cumulative dose of buprenorphine reached 0.9 mg (approximately 9 mcg/kg). This is consistent with a previous report that in methadone overdose, 10 mcg/kg of IV buprenorphine caused no withdrawal, and 15 mcg/kg resulted in, at most, mild withdrawal symptoms²⁴ The withdrawal occurred 2 hours after a dose of IV buprenorphine, much later than the expected brain tissue peak concentration.²⁵ We therefore speculate that the withdrawal was related to the central nervous system level of methadone, rather than of buprenorphine. Methadone was administered Q12h, and the withdrawal episode occurred at the tail end of its dosing interval at approximately 10 hours. We wonder whether the withdrawal could have been avoided if we chose a Q8h dosing schedule of methadone.

Our micro-induction protocol was completed over just 4 days. In comparison, standard induction for an inpatient on 80 mg of methadone would take at least 2 weeks to complete.

Conclusion

We report a case of successful and well-tolerated buprenorphine induction using a novel inpatient

IV micro-dosing 4-day protocol in a patient on methadone. We believe this to be a promising approach and further investigation into even shorter protocols using IV buprenorphine is warranted.

References

1. Liebschutz JM, Crooks D, Herman D, et al: Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med* 2014; 174:1369–1376
2. Lee JD, Nunes EV, Novo P, et al: Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 2018; 391:309–318
3. Coe MA, Lofwall MR, Walsh SL: Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med* 2019; 13:93–103
4. Dahan A, Yassen A, Romberg R, et al: Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006; 96:627–632
5. Kraus ML, Alford DP, Kotz MM, et al: Statement of the American Society of Addiction Medicine consensus panel on the use of buprenorphine in office-based treatment of opioid addiction. *J Addict Med* 2011; 5:254–263
6. Rosado J, Walsh SL, Bigelow GE, Strain EC: Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. *Drug Alcohol Depend* 2007; 90:261–269
7. Hämmig R, Kemter A, Strasser J, et al: Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the “Bernese method.” *Subst Abuse Rehabil* 2016; 7:99–105
8. Becker WC, Frank JW, Edens EL: Switching from high-dose, long-term opioids to buprenorphine: a case series. *Ann Intern Med* 2020; 173:70–71
9. Rozylo J, Mitchell K, Nikoo M, et al: Case report: successful induction of buprenorphine/naloxone using a microdosing schedule and assertive outreach. *Addict Sci Clin Pract* 2020; 15:2
10. Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P: Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. *Am J Addict* 2019; 28:262–265
11. Tang VM, Lam-Shang-Leen J, Brothers TD, et al: Case series: limited opioid withdrawal with use of transdermal buprenorphine to bridge to sublingual buprenorphine in hospitalized patients. *Am J Addict* 2020; 29:73–76
12. Subutex [Prescribing Information]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020732s018lbl.pdf; 2015
13. Terasaki D, Smith C, Calcaterra SL: Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. *Pharmacotherapy* 2019; 39:1023–1029
14. Medi-Span Price Rx. Available from: <https://pricerx.medspan.com/login.aspx>; 2020
15. Raffa RB, Haidery M, Huang H-M, et al: The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther* 2014; 39:577–583
16. Mendelson J, Upton RA, Everhart ET, Jacob P III, Jones RT: Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; 37:31–37
17. Kuhlman JJ, Lalani S, Maglulio J, et al: Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol* 1996; 20:369–378
18. Bai SA, Xiang Q, Finn A: Evaluation of the pharmacokinetics of single- and multiple-dose buprenorphine buccal film in healthy volunteers. *Clin Ther* 2016; 38:358–369
19. Ghosh SM, Klaire S, Tanguay R, Manek M, Azar P: A review of novel methods to support the transition from methadone and other full agonist opioids to buprenorphine/naloxone sublingual in both community and acute care settings. *Can J Addict* 2019; 10:41–50
20. Clarke H, Weinrib A, Kotteeswaran Y, Katz J, Yu A, Tanguay R: Remote buprenorphine-naloxone initiation as an essential service for people with chronic pain and opioid dependence during the COVID-19 pandemic: case reports, clinical pathways, and implications for the future. *Can J Pain* 2020. <https://doi.org/10.1080/24740527.2020.1795634> [Epub ahead of print]
21. Zacny JP, Hill JL, Black ML, Sadeghi P: Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in normal volunteers. *J Pharmacol Exp Ther* 1998; 286:1197–1207
22. Comer SD, Sullivan MA, Walker EA: Comparison of intravenous buprenorphine and methadone self-administration by recently detoxified heroin-dependent individuals. *J Pharmacol Exp Ther* 2005; 315:1320–1330
23. Chilcoat HD, Amick HR, Sherwood MR, Dunn KE: Buprenorphine in the United States: motives for abuse, misuse, and diversion. *J Subst Abuse Treat* 2019; 104:148–157
24. Zamani N, Buckley NA, Hassanian-Moghaddam H: Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial. *Crit Care* 2020; 24:1–9
25. Kalluri HV, Zhang H, Caritis SN, Venkataramanan R: A physiologically based pharmacokinetic modelling approach to predict buprenorphine pharmacokinetics following intravenous and sublingual administration. *Br J Clin Pharmacol* 2017; 83:2458–2473