ADDICTIVE DISORDER TREATMENTS

mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Intolerance of sublingual buprenorphine-naloxone during induction in a patient with end-stage liver disease: A case report

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How to cite: Behan J, Geier M. Intolerance of sublingual buprenorphine-naloxone during induction in a patient with end-stage liver disease: A case report. Ment Health Clin [Internet]. 2016;6(3):131-3. DOI: 10.9740/mhc.2016.05.131.

Abstract

Introduction: Sublingual buprenorphine is indicated for opioid dependence. It comes in 2 formulations: a mono buprenorphine product (BUP) and a combination product containing naloxone (BUP-NAL), which functions as an abuse deterrent. Sublingual naloxone does not reach clinically significant levels except in cases of hepatic impairment, where its metabolism can be impaired. Substantial naloxone accumulation could block the therapeutic effects of buprenorphine. The risk of hepatic impairment is elevated in the opioid dependence population, and our case highlights the need for careful evaluation of hepatic function and consideration of BUP.

Case/Results: We report a patient with end-stage liver disease who began BUP-NAL induction with modest improvement on treatment day 1 followed by sustained withdrawal after receiving an observed dose on day 2. He returned to the clinic 2 days after his second successive day of BUP-NAL, vomiting and complaining of persistent withdrawal. To avoid potential accumulation of naloxone, the patient was eventually switched to and stabilized on BUP with good response.

Discussion/Conclusion: The clinical course this patient experienced during induction makes a case that naloxone can accumulate and interfere with the effectiveness of buprenorphine in the presence of liver dysfunction. Our case highlights the need for consideration of BUP in circumstances where patient safety and effective treatment outweigh the risks of prescribing a product with abuse deterrent properties.

Keywords: buprenorphine-naloxone, Subutex, Suboxone, opioid use disorder, heroin addiction, liver impairment, end-stage liver disease, hepatic dysfunction, induction

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Introduction

This report describes a case of a 42-year-old male with end-stage liver disease (ESLD) who poorly tolerated the combination of buprenorphine-naloxone (BUP-NAL) during induction and responded favorably when switched to the mono buprenorphine product (BUP) for maintenance. Our case highlights the need for careful evaluation of liver function and consideration of BUP in circumstances where patient safety and effective treatment might outweigh the risks of prescribing a product with abuse deterrent properties.

Sublingual (SL) buprenorphine is a life-changing medication for many and an evidence-based treatment for opioid use disorder. It offers individuals an alternative to methadone for medication-assisted treatment with the advantage of reduced legal regulations.[1] Five SL buprenorphine formulations are currently available in the United States. The most clinically relevant difference is between BUP, which contains only the mu opioid receptor partial agonist buprenorphine, and the combination product BUP-NAL which has the addition of the mu opioid receptor antagonist naloxone.[1,2] When taken

sublingually, in most cases, the naloxone in the combination product does not reach appreciable levels and has no clinical effect. However, when BUP-NAL is injected, the naloxone causes immediate severe opioid withdrawal in opioid-dependent patients, working as an abuse deterrent.[1,3]

An exception may exist in patients with moderate to severe hepatic impairment, where elimination of SL naloxone can be substantially decreased. In a pharmacokinetic single-dose study of patients with severe hepatic impairment, it was found that SL buprenorphine exposure increased as much as 3-fold, whereas naloxone increased 10-fold.[4] In patients with severe hepatic impairment (Child-Pugh class C), Reckitt Benckiser Pharmaceuticals (Slough, United Kingdom) has reported increases in exposure of the concentration maximum as high as 72% in buprenorphine and 1302% of naloxone, significant increases in half-life were also observed.[5] The disproportionate increase in naloxone exposure could compromise the efficacy of buprenorphine. The drug manufacturer recommends avoiding the combination product in severe hepatic impairment and cautions its use in cases of moderate impairment.[4,5] It is well recognized that the opioid use disorder population is at an elevated risk of hepatic impairment, with study cohorts reporting 64% to 100% rates of hepatitis C infection. The presence of comorbid alcohol use disorder often presents additional risk.[1,6-10] Because of the increased risk of diversion and misuse, providers may feel resistant to prescribing BUP despite the potential for adverse outcomes.

The presence of the antagonist in BUP-NAL makes it an attractive treatment option for many clinicians who are concerned about parenteral abuse and diversion. Misuse was substantiated in a 2001 survey of 343 French individuals with intravenous drug use of which one-third reported injecting BUP.[1,11,12] Almost all buprenorphine-related deaths have been attributed to parenteral administration in addition to the presence of benzodiazepines. For these reasons, the Substance Abuse and Mental Health Services Administration clinical guidelines for the use of buprenorphine in the treatment of opioid addiction recommend using BUP-NAL as the first-line treatment for both induction and maintenance in most patients.[1,13] Pregnant patients are defined as a special population that should receive BUP. It is advised that patients switching from long-acting opioid agents (eg, methadone) be given consideration for BUP during the first 2 days of induction; however, patients with hepatic impairment are not listed as a group that should receive special consideration for BUP treatment at any point.[1] Notably, these guidelines were last updated in 2004, which was prior to pharmacokinetic studies of BUP-NAL products in patients with varied degrees of hepatic impairment.[1]

Case Study

We report a patient with ESLD who engaged in an outpatient sublingual buprenorphine induction program for the treatment of opioid use disorder. At enrollment, he had a lengthy history of substance use including heroin, alcohol, methamphetamines, and marijuana. His medical history was significant for hepatitis C virus secondary to intravenous drug use and alcoholic liver disease with cirrhosis diagnosed 3 years prior. Hepatic complications included ascites and portal hypertension, which were being controlled with furosemide and propranolol. His most recent laboratory values included a low albumin level of 2.9 (g/dL) and elevated international normalized ratio of 1.3 with prothrombin time of 15.5 seconds, he had a Child-Pugh score of 7 and classification of B, indicating moderate hepatic impairment.[14]

On induction day 1, he presented in mild withdrawal with a clinical opiate withdrawal scale (COWS) score of 6. He was given a total of 16 mg to 4 mg of BUP-NAL and instructed to take 4 mg to 1 mg every 4 to 6 hours as needed for opioid withdrawal symptoms. He relapsed to heroin after his visit and delayed his induction to the following day at 2:00 AM. On day 3, he returned to the clinic in the morning in mild withdrawal, reporting taking his last dose of BUP-NAL at 7:00 AM that morning. Seeming to have tolerated the medication, he was given an observed dose of 8 mg to 2 mg BUP-NAL and instructed to come back the next day. He returned on day 5 and vomited at clinic and complained of persistent withdrawal symptoms consisting of malaise, neck soreness, constant nausea, anorexia, dizziness, and diarrhea with tarry stools for the past 2 days. He reported injecting a *small* amount of heroin to treat his sustained diarrhea at 1 AM that night with no relief. He reported that the BUP-NAL he had taken throughout the week helped relieve his withdrawal symptoms but only for brief periods. His COWS score was 9, and he was given a 12 mg to 3 mg BUP-NAL observed dose. After 40 minutes, his COWS score was 4, and his nausea persisted. He was given 4.5, 8-mg to 2-mg tablets to take home and instructed to take 1 tablet twice daily and return in 3 days. In addition to orthostasis and tarry stools, the client was sent to the emergency room, where he was admitted and found to have gastric erosion but no active gastrointestinal bleed. The patient was hospitalized for several days and returned to the clinic 5 days later reportedly taking variable amounts of BUP-NAL over 5 days, with a now favorable response. Owing to concerns for his hepatic impairment leading to accumulation of naloxone and because of the opioid withdrawal symptoms described the morning of day 4 to 5, he was switched to BUP at 16 mg daily. The patient responded to BUP with reduced cravings and opioid withdrawal and continued on it for maintenance.

Discussion

Induction with 2 days of successive dosing with BUP-NAL in a patient with ESLD resulted in 2 days of sustained withdrawal with subsequent relapse to heroin. This case demonstrates that hepatic impairment potentially causes accumulation of naloxone, which results in uncontrolled opioid withdrawal during induction. This patient was classified as having ESLD manifested by a combination of alcoholic liver disease and hepatitis C virus. He presented to the clinic with a Child-Pugh score of B, implicating only moderate impairment and no clear contraindication for the use of BUP-NAL. The clinical course this patient experienced during induction makes a case that naloxone can accumulate and interfere with the effectiveness of buprenorphine in the presence of liver dysfunction.

Conclusion

The BUP-NAL package insert provides some guidance as to possible alterations in drug metabolism in hepatic impairment categorized by Child-Pugh scores and recommends it be avoided in patients with a Child-Pugh C designation. Limitations in guidance exist for patients with moderate impairment as there is no clear consensus. Controversy over the accuracy of Child-Pugh scores to determine the level of hepatic impairment also exists, as a great deal of interindividual results exist in terms of the ability to metabolize drugs.[15] This leaves clinicians with the difficult task of assessing the role liver function plays in response to treatment on a case-by-case basis. It seems conceivable that cases of moderate hepatic impairment receive consideration of BUP during the induction phase, and possibly as a maintenance option in certain cases.

Limitations of this report include poor follow-up and medication adherence, intermittent heroin use, and medical complication requiring hospitalization during induction. Starting BUP after probable abstinence from heroin and after acute withdrawal had ceased may have been responsible for the favorable response. The limited response and seemingly sustained withdrawal symptoms this patient experienced during induction with BUP-NAL suggest naloxone accumulation as a possible explanation. Owing to the complicated nature of this case, no firm conclusions can be drawn, but with the high prevalence of hepatic impairment in the opioid use disorder population, it calls attention to the need for more research and clinical guidance in this area.

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