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Case Report open access

Iatrogenic Opioid-withdrawal Induced by Contrave®

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Abstract

Introduction: New medications for the management of obesity are rapidly coming through the drug design pipeline. Among those recently approved is Contrave®, [naltrexone/bupropion] which has shown a modest and clinically relevant weight loss. We report two cases of naltrexone-induced opioid withdrawal resulting from the prescription of Contrave® to opioid-dependent patients.

Case details: Patient 1 was a 59-year-old male with chronic pain prescribed morphine 60 mg and oxycodone 30 mg daily. He was prescribed Contrave® as adjunct to lifestyle modifications in the management of his obesity. Withdrawal symptoms precipitated within a few hours of his first dose. The resultant vomiting and anxiety led to patient distress and an emergency department visit. Patient 2 was a 42-year-old female former heroin user on methadone maintenance 90 mg daily. She was started on Contrave® as an effort towards meaningful weight loss. Within the first hour after her first dose she began to have withdrawal symptoms. On arrival at the ED the patient was agitated and nauseated, and required treatment with IV fluids, lorazepam, and ondansetron for her symptoms.

Discussion: As a naltrexone-containing product, there is the potential for the induction of withdrawal in opioid-dependent patients. Physicians may be unaware of the inclusion of this opioid antagonist in the newly marketed medication or overlook the ability of naltrexone to produce acute withdrawal. Pharmacy profiles might not reveal that a patient is on methadone maintenance or using opioid medications illicitly. Patients may not always provide a complete medication history, and may not report opioid usage to their health care providers without direct questioning. Thus, clinicians and pharmacists must ask about the use of other medications and or illicitly used drugs and caution patients about this potential interaction.

Introduction

More than a third of adults and nearly a fifth of children in the United States are obese [1]. Increased Body Mass Index (BMI) is a risk factor for many pathological states and is known to increase all-cause mortality. Many management options exist for the treatment of patients with obesity. These include conservative approaches such as lifestyle modifications (diet and exercise) and behavioral therapy [2]. More radical management methods such as bariatric surgery are reserved for patients who are morbidly obese and recalcitrant to lifestyle recommendations [3]. Patients in need of moderate weight loss have historically been managed with various pharmacologic modalities.

Three medications have been licensed for use in weight reduction since 2010: (Belvic® [locaserin], Contrave® [naltrexone/bupropion], and Qsymia® [phentermine/topiramate]). The newest of these, Contrave®, is a combination of naltrexone 32 mg, a nonselective opioid receptor antagonist, and bupropion 360 mg, a weak blocker of dopamine norepinephrine and serotonin reuptake, in a sustained release formulation. Bupropion is thought to induce weight loss by increased activity of dopamine and norepinephrine on pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus, which are known to be involved in regulation of energy balance [4,5]. Physiologic action of endogenous leptin at this site has been identified as having an anorexigenic effect [5,6]. Additionally, since POMC neurons are known to be inhibited by endogenous opioids such as β-endorphin, use of opioid antagonists such as naltrexone was pursued as a means of augmentation in this central nervous system-based approach to weight loss [4,5]. Though neither of these drugs is individually new to the market, their combined use for the management of obesity represents a novel approach. This combination has been shown to overcome the classic weight loss plateau seen with some monotherapeutic approaches [4].

With the release of any new medication is the potential for unforeseen side effects, complications, and interactions. Early identification of these new issues relies upon the cooperation of providers, manufacturers and government regulatory agencies in post-marketing surveillance. Recently, the New Jersey Poison Information and Education System, was consulted about two patients with suspected Contrave®-induced opiate withdrawal. Both of these cases resulted in significant patient distress and preventable utilization of medical resources. In one case, the prescribing physician was unaware of the patient's participation in methadone maintenance. In the other,

the prescribing physician and pharmacist failed to appreciate the potential interaction in spite of adequate patient records.

Case Reports

Patient 1 was a 59-year-old male with a history of a chronic pain syndrome who was on 60 mg morphine and 30 mg oxycodone daily for pain management. The patient's outpatient physician prescribed Contrave®, naltrexone 8 mg/ bupropion 90 mg in order to help the patient attain his weight loss goals. Within 24 hours of taking the new medication, the patient began to vomit and experienced anxiety severe enough to prompt a visit to the ER. On arrival the patient's vitals were as follows: BP: 158/69, Pulse: 79, T: 99.2, O_2 saturation: 98% on room air. He was treated in the ER with IV fluids, benzodiazepines, and morphine and counseled on the interaction of his medications. The patient was subsequently discharged with instruction to stop the new medication and follow up with his doctor.

Patient 2 was a 42-year-old female on methadone maintenance 90 mg daily who was started on Contrave®, naltrexone 8 mg/ bupropion 90 mg, as an adjunct to lifestyle modifications for weight control. One hour after taking her first dose the patient began to have withdrawal symptoms. Upon reporting to the ER the patient was agitated and nauseated and required treatment with IV fluids, lorazepam, and ondansetron. Her vital signs were as follows: BP: 118/70, Pulse: 80, Respiration rate: 20, Afebrile. O_2 saturation: 100% on room air. Since she was already experiencing withdrawal, there was a discussion with the patient about the option of not restarting methadone maintenance. The patient and attending physician came to an agreement that methadone maintenance treatment would be resumed. The patient's dose was confirmed with the methadone clinic and therapy resumed at a dose of 90mg daily in the hospital. Her withdrawal symptoms abated and she was discharged home with instruction to stop the new medication.

Discussion

Study of the endocrine and metabolic disturbances have led to the acceptance of obesity as a chronic disease [2]. Like other chronic diseases, treatment protocols often begin conservatively, increasing in invasiveness only as necessary. As appealing as conservative treatments like diet and exercise may be, less than half of patients will achieve the minimal weight loss considered to have a benefit in decreasing the risk of cardiovascular disease (5% loss of body weight at 4 years) [7]. In fact, in patients with severe obesity (i.e. BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with manifest serious comorbidity), non-operative treatments have been shown to be ineffective [8]. Surgical management is associated with the highest success, with loss of 30-70% excess weight being typical [3]. However, bariatric surgery also brings attendant risks such as malnutrition, fat malabsorption, and syndromes of vitamin and mineral malabsorption, along with the risks of any surgical procedure [3].

Pharmacologic intervention in patients with a need for treating obesity provides the potential for weight reduction in individuals in whom the risks of surgical management are too high. The advent of newer medications, including combination naltrexone/bupropion will hopefully lead to better patient outcomes. However, as these two cases demonstrate widespread adoption of these new treatment protocols needs to be preceded by adequate physician and patient education about the potential for drug interactions. Use of opioid-antagonists concurrently with opioids often results in systemic withdrawal symptoms such as nausea, vomiting, diarrhea, diaphoresis, anxiety, and abdominal cramping. The patients we report developed some of these symptoms of withdrawal and needed hospital care. Although opioid withdrawal syndrome is not life-threatening, the events were indeed disturbing to the individuals involved and produced measureable health care costs. These episodes were totally preventable, had the prescribing physicians or pharmacists been aware of the patient's concurrent opioid use. A careful history and check of the patient's pharmacy profile might have revealed their chronic use of an opioid and relative contraindication of the bariatric medication.

Patients who misuse or abuse opiates of all types may be another group at risk for these drug interactions when prescribed naltrexone/ bupropion. Patients who are using drugs illicitly are likely to be reticent about revealing this information to their physicians. The likelihood of one of these patients being prescribed naltrexone-containing weight loss drugs should not be underplayed. Illicit opioid abuse or dependence is self-reported in almost one percent of the population [9]. There are over three hundred thousand patients on methadone maintenance in the United States, and an additional thirty thousand are on buprenorphine replacement therapy [10]. The potential of naltrexone to antagonize opiates is well known. In fact, the in-box medication instructions for Contrave® recommend that patients formerly on any opioid stop its use 7-10 days prior to beginning therapy. However patients who have been on buprenorphine or methadone maintenance therapy may not mention this to their health care providers unless specifically asked. Without knowing of the existing maintenance therapy a physician may prescribe this combination medication and put the recipient in danger. The likelihood of encountering a patient who has some contact with opioid medications is high in the United States. Some of them may be receiving pain medication from friends/family, using heroin, on methadone, or taking other opioids for various reasons, including abuse. Hence, all patients to be placed on this new medication should have careful medication/drug histories taken, and patient education about the potential for withdrawal.

One potential though costly way to avoid these types of interactions might be to obtain a urine drug screen for opiates before a prescription for this medication is written. While this screening might prevent some potential cases, patients abusing synthetic opioids such as fentanyl, buprenorphine, and tramadol may be missed since the standard urine drug screen is not able to pick them up [11]. Prescribing physicians and dispensing pharmacists must ask about potential interactions with other medications and or illicitly used drugs and caution patients about this potential interaction.

Conclusion

We report 2 cases of apparent withdrawal from their chronic opioid dependence from the coincidental use of a new weight-reducing medication containing the opioid-antagonist naltrexone. Continued monitoring for these types of events should guide future recommendations on screening and patient education.

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