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CLINICAL CASE ROUNDS

A Case of Constipation and Gastrointestinal Retention of Lisdexamfetamine Dimesylate Capsules in an 11-Year-Old

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Abstract

Attention deficit hyperactivity disorder (ADHD) has a worldwide prevalence of 5.29% and stimulant medications are considered first-line treatment. Common adverse events with these medications include decreased appetite, increased sleep latency, tics, abdominal pain, and weight loss. Lisdexamfetamine dimesylate (LDX) is a stimulant used for treating ADHD and may lead to gastrointestinal, among other adverse effects. In this report, we present a case of constipation and retention of LDX capsules in the gastrointestinal tract. An 11-year-old male with a diagnosis of ADHD was being treated with once daily LDX 30 mg in our clinic. After about ten weeks of treatment, he was brought to an emergency department due to epigastric pain and constipation. An abdominal X-ray was significant for the presence of approximately 20 capsules in the large intestine. He was admitted to the pediatric gastroenterology service. Following management with two saline enemas, fewer capsules were seen on repeat X-ray. The patient was observed overnight, advised to discontinue LDX and discharged home in a stable condition. LDX may be associated with constipation and retention of intact capsules in the gastrointestinal tract. Further research is warranted to exclude the risk of sympathomimetic toxidrome if intact LDX capsules simultaneously disintegrate in the gastrointestinal tract.

Key Words: constipation, retention, lisdexamfetamine, ADHD, stimulant

Résumé

Le trouble de déficit de l'attention avec hyperactivité (TDAH) a une prévalence mondiale de 5,29 % et les médicaments stimulants sont considérés le traitement de première intention. Les effets indésirables communs de ces médicaments sont notamment un appétit réduit, le délai d'endormissement accru, les tics, la douleur abdominale, et la perte de poids. Le dimésylate de lisdexamfétamine (LDX) est un stimulant utilisé pour traiter le TDAH et peut entraîner un effet gastro-intestinal, entre autres effets. Dans cette étude, nous présentons un cas de constipation et de rétention de capsules de LDX dans le tractus gastro-intestinal. Un garçon de 11 ans ayant reçu un diagnostic de TDAH était traité par LDX 30 mg une fois par jour dans notre clinique. Après environ 10 semaines de traitement, il a été amené à un service d'urgence en raison de douleur épigastrique et de constipation. Une radiographie abdominale a révélé la présence de quelque 20 capsules dans le gros intestin. Il a été hospitalisé dans un service de gastro-entérologie pédiatrique. Après une prise en charge avec deux lavements de solution salée, moins de capsules étaient visibles à la radiographie répétée. Le patient a

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été gardé sous observation pour la nuit, on lui a conseillé de cesser le LDX et il a eu son congé à la maison dans un état stable. Le LDX peut être associé à la constipation et à la rétention de capsules intactes dans le tractus gastro-intestinal. Il faut d'autre recherche pour exclure le risque d'un toxidrome sympathomimétique si des capsules de LDX intactes se désintègrent simultanément dans le tractus gastro-intestinal.

Mots clés: *constipation, rétention, lisdexamfétamine, TDAH, stimulant*

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common mental health diagnosis with a worldwide prevalence of 5.29% (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007). It is effectively managed with psychopharmacology alone or in combination with behavioral therapy (Felt, Biermann, Christner, Kochhar, & Harrison, 2014). First-line treatments include central nervous system (CNS) stimulants with a reported short-term therapeutic response close to 70% (May & Kratochvil, 2010). The most common adverse effects (AE) of CNS stimulants in ADHD treatment include sleep disturbances, decrease in appetite (Wolraich, McGuinn, & Doffing, 2007), hypertension, and tachycardia (Levy, 1993). Gastrointestinal (GI) AEs are less common with nausea and abdominal discomfort being most prevalent (Wolraich, McGuinn, & Doffing, 2007). Despite constipation being reported with other stimulants such as dextroamphetamine and dextroamphetamine-amphetamine mixed salts (Lakhan & Kirchgessner, 2012), it has not been identified as a potential AE of lisdexamfetamine (LDX).

LDX is a pro-drug used for treatment of ADHD in children aged six years and above as well as adults (with maximum daily dosage of 60 mg in Canada and 70 mg in the USA). It is absorbed by active transport across the small intestine and hydrolyzed to form dextroamphetamine after contact with red blood cells. The mean half-life ($t_{1/2}$) of LDX is approximately 1.6 hours (Hutson, Pennick, & Secker, 2014). Hydrolysis of LDX into dextroamphetamine allows for slower appearance of dextroamphetamine in the blood and consequently the brain tissue, a pharmacokinetic characteristic that allows for once daily administration without other extended release technology (Hutson, Pennick, & Secker, 2014). Medication efficacy is evidenced by significant improvement in ADHD Rating Scale Version IV and the Conners' Parent Rating Scale (Biederman, Krishnan, Zhang, McGough, & Findling, 2007). The AEs most commonly reported (>5%) were decreased appetite, increased sleep latency, tics, abdominal pain and weight loss (Coghill, Caballero, Sorooshian, & Civil, 2014). We describe the first reported case of constipation and gastrointestinal retention with LDX with permission from the parent and patient, to publish this case.

Case presentation

An 11-year-old white male with a past history significant for the diagnosis and management of ADHD, presented to our clinic in order to establish ongoing care. His chief complaints were inability to concentrate and hyperactivity which affected his school performance. He also reported sad mood and sleep difficulty, but denied other symptoms suggestive of major depressive disorder. His mother described episodes of anger and symptoms suggestive of oppositional defiant disorder.

At the time of his initial assessment at our clinic, he was taking immediate release mixed amphetamine salts 30 mg twice daily (available in the United States but not Canada) for ADHD and over the counter melatonin 10 mg as needed at nighttime for insomnia. He was previously prescribed immediate-release clonidine 0.2 mg at bedtime for difficulty with sleep. Despite adequate sleep hygiene, he complained of ongoing sleep disturbance associated with ADHD. Therefore, based on patient and parent's preference, clonidine was resumed at 0.05 mg at bedtime then titrated to 0.1 mg with a positive response. However, ADHD symptoms were not controlled and LDX 30 mg daily was started. Clonidine had been titrated two weeks prior to this and was continued at 0.1 mg at bedtime. The patient also continued to take melatonin at bedtime as needed. Upon follow up, his ADHD symptoms were reported to be well controlled by the patient, his mother, and teachers.

Around ten weeks after these medication changes, he was brought to an emergency department (ED) by his mother. The primary reason for this ED visit was one-week history of epigastric pain and worsening constipation. She reported that he had a few episodes of diarrhea preceding the constipation. She also endorsed him having loose liquid like stools and fecal incontinence alongside the constipation, during the prior 48 hours. The patient reported seeing pieces of orange capsules in his stool for a couple of weeks prior to the start of epigastric pain and constipation. About a week prior to presentation to the ED, he began experiencing abdominal pain with bowel movements. His mother noted that he was becoming lethargic prior to the ED visit. She reported safekeeping and administering medication herself and discounted any possibility of acute ingestion or misuse.

An abdominal antero-posterior supine X-ray (Figure 1) obtained in the ED was significant for whole and remnants of approximately 20 capsules in the large intestine. As vital signs were found to be stable, the patient was discharged to home with symptomatic treatment.

In less than 24 hours, the patient experienced worsening abdominal pain, called his primary care provider, and subsequently presented to the ED for the second time for further evaluation. The mother denied any history of chronic constipation or gastrointestinal illnesses. Physical and mental status exams were grossly normal in the ED. Vital signs were stable and within the normal range. Complete blood count, urine drug screen, thyroid panel, and tissue transglutaminase antibody screen were unrevealing. Comprehensive metabolic panels revealed slight hypernatremia (148 mmol/L), anion gap of 15 and normal liver enzymes. The slight hypernatremia was most probably related to dehydration in the setting of clear fluid diarrheal episodes. Prior to the constipation and diarrhea episodes, the patient was not noted to be dehydrated. An interval abdominal x-ray was remarkable for a decrease in the number of capsules seen in the colon compared to previous ED visit X-ray. His vitals and presentation were not concerning for increased sympathetic tone. However, due to the presence of presumed LDX capsules in the large intestine, the poison control center recommended a bowel cleanout. Thus, he was admitted to the pediatric gastroenterology service. Intravenous fluids were started and two saline enemas were administered separated by two hours. A nasogastric tube was placed and bowel cleanout using polyethylene glycol 3350 and electrolytes oral solution was commenced. A follow up abdominal X-ray revealed further decrease in the number of capsules seen in the large intestine. He was observed overnight and eventually discharged with a prescription for polyethylene glycol. He was also advised to discontinue LDX and we reported the adverse event to the FDA.

On follow up appointments with pediatric gastroenterology and our psychiatry clinics, the patient denied abdominal pain and constipation. He was restarted on the immediate release mixed amphetamine salts 20 mg once daily. Mixed amphetamine salts was titrated up to 30 mg in the morning and 10 mg at 1pm with good symptom control, without any significant side effects or constipation.

Discussion

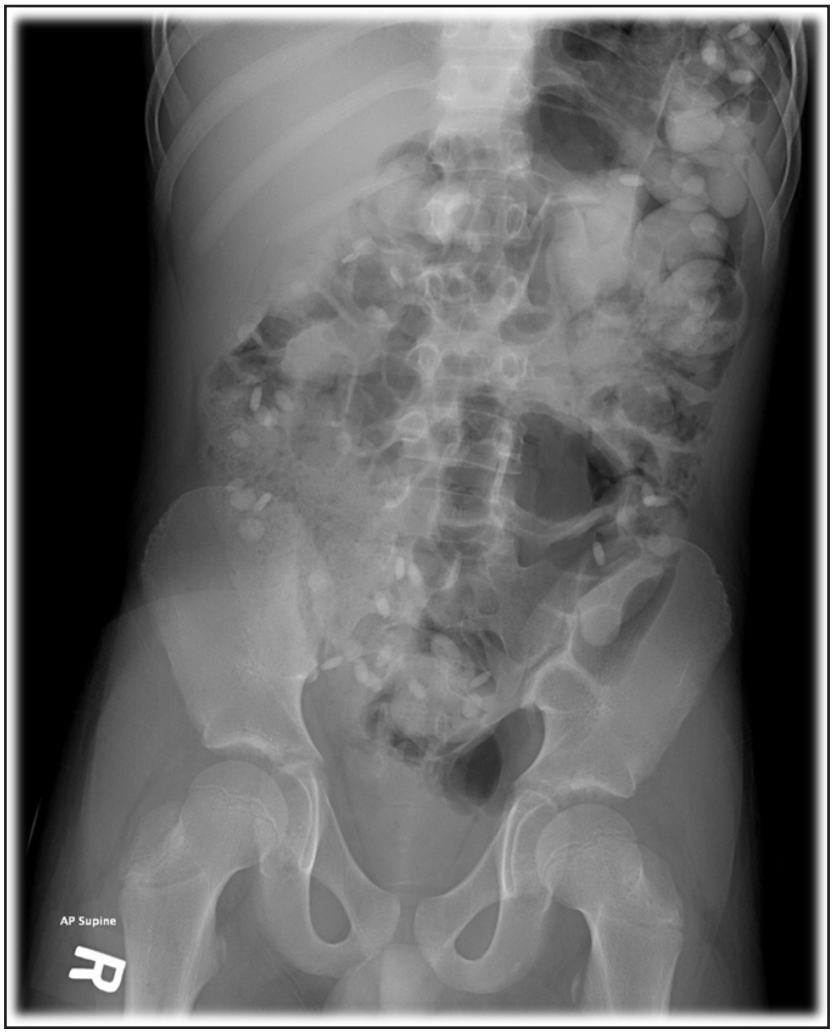
Extended release stimulants have long been used in the treatment of ADHD. Their safety and tolerability profile in treatment of ADHD is similar to other stimulants. A possible advantage of LDX is the rate of non-medical use/abuse is noted to be lower than that for immediate release stimulants and lower than or equivalent to other long-acting stimulant formulations (Coghill, Caballero, Sorooshian, & Civil, 2014). For our patient we also noted that his symptoms responded well to a lower dose of LDX compared to the maximum daily dose of mixed amphetamine salts.

Adverse effects with LDX are commonly noted to be decrease in appetite, difficulty sleeping, abdominal pain, and weight loss (Coghill, Caballero, Sorooshian, & Civil, 2014). The most common GI adverse effects reported for LDX in ADHD studies include diarrhea, dry mouth, nausea, upper stomach pain and vomiting (Coghill, Caballero, Sorooshian, & Civil, 2014). Constipation may be caused by LDX in nearly 6% of binge eating disorder (BED) patients while constipation occurred only in 1% of BED patients given placebo (Kornstein, Bliss, Kando, & Madhoo, 2019). It appears that LDX, due to possible anticholinergic properties, can also cause constipation in individuals without moderate to severe BED. Despite the fact that clonidine can induce constipation, our patient tolerated a higher dose of clonidine in the past without developing this AE. Also, clonidine was started and titrated prior to starting LDX with no evidence of constipation. Our literature search did not reveal prior reports of constipation and retention of LDX capsules in the gastrointestinal tract secondary to its use in the ADHD population. It is worth noting, that the AE developed several weeks after starting LDX without dose changes in either clonidine or LDX. It is also unclear whether this may have been an additive AE of the medication combination. The apparent retention of intact LDX capsules could conceivably cause a decrease in efficacy, while exposing the patient to a risk of sympathomimetic toxidrome, in case the accumulated capsules disintegrated simultaneously.

Shire Pharmaceuticals in the United States, manufacturer of LDX, was contacted to report this AE. They were not aware of any other cases in which LDX capsules may have been retained in the lower gut and did not ask to examine the capsules. The patient was dispensed two 30-day-supply of the medication one month apart which begs the question whether a certain batch of LDX capsules was responsible for the adverse event. We were advised that the LDX capsule shell is primarily composed of gelatin which is readily soluble in aqueous systems and GI fluids. There are quality control tests performed on the empty capsules and those filled with the constituents of the medication product, to ensure the capsules disintegrate quickly, usually within 15 minutes of swallowing (Personal communication with Shire Pharmaceuticals, US).

Some extended-release formulations, such as those using an osmotic-release delivery system, have the possibility of causing “ghost pills” (Wheless & Phelps, 2018;

Figure 1. An abdominal antero-posterior supine X-ray obtained in the ED was significant for whole and remnants of approximately 20 capsules in the large intestine



Tungaraza, Talapan-Manikoth, & Jenkins, 2013; Gabor, Fillafer, Neutsch, Ratzinger, & Wirth, 2010). This phenomenon occurs when the shell of the medication does not disintegrate or digest completely; instead, the shell passes through the stool. In these formulations, the presence of "ghost pills'' does not indicate an absorption problem. One example of such a medication is osmotic-release oral system (OROS) methylphenidate tablet, which does not dissolve completely in the gut while the medication is released. The empty shell may be noticed in feces which is considered normal (FDA Access Data Website, 2007). If a patient taking these medications becomes constipated, the capsules or tablets can become retained in the bowel. According to the LDX medication use guide, the capsule and disintegrate are not commonly seen in the stool (Shirecontent Website, 2017). In our case, some capsules appeared to be intact on the abdominal x-ray but the report that the patient's ADHD symptoms remained well-controlled supports the likelihood that the active ingredient from some of the capsules was released and absorbed as intended.

One of the first-line treatments for individuals with ADHD is LDX (Hutson, Pennick, & Secker, 2014). Although primarily composed of gelatin, which usually dissolves in aqueous solutions, LDX capsules may be retained in the gastrointestinal tract. Thus, providers need to be aware of adverse events such as epigastric pain, constipation, and retention of capsules with the use of this medication in children with

ADHD. Further studies may be warranted to explore constipation as a possible adverse effect of LDX, versus retention of capsules due to underlying gastrointestinal dysmotility. In the meantime, the chewable form of LDX is an alternative safer form that can be used to avoid the reported AE (Shirecontent Website, 2017). From a safety perspective additional research is also needed to rule out a risk of a potential toxidrome, if the intact capsules containing active ingredient were to simultaneously disintegrate in the gastrointestinal tract.

Conflicts of Interest:

The authors have no financial relationships to disclose.

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