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A Severe Case of Dexamethasone-Induced Hiccups Associated with Gastrointestinal Upset after Lumbar Epidural Administration

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Background: Hiccups are a common and often harmless spasm of the diaphragm and respiratory organs. Hiccups typically resolve spontaneously and without need for medical intervention. However, there have been rare reported instances where hiccups could be present as an adverse effect of dexamethasone, causing drastic and intolerable effects for a prolonged period of time.

Case Report: A 59-year-old Caucasian man came to the pain management clinic and was given an epidural, which consisted of 10 mg dexamethasone and 1 mL bupivacaine. Hours later, the patient began having severe hiccups. The hiccups caused severe abdominal pain, disabled him from eating and drinking, and prevented him from sleeping. The hiccups lasted for around 18+ hours, having a sporadic resolution on the second day.

Conclusions: Dexamethasone is often mixed with local anesthetics to treat chronic pain. It is worthwhile to highlight the rare incidence of developing severe hiccups as an adverse effect of dexamethasone administration.

Key words: Dexamethasone, epidural, bupivacaine, hiccups

BACKGROUND

Hiccups are an involuntary spasm of the diaphragm and respiratory organs, with a sudden closure of the glottis. This sudden closure of the glottis leads to the common sound that is often associated with hiccups (1). Hiccups are common and they are generally considered harmless, as there are many day-to-day activities that could cause an acute episode of hiccups, such as drinking carbonated beverages, experiencing excitement or stress, or eating your food too quickly. Oftentimes, these hiccups resolve on their own within a couple of minutes and usually do not cause any severe distress. However, there have been rare but reported instances in the field of pain management where intolerable hiccups could develop as an adverse effect of medications, such as dexamethasone. Dexamethasone is a corticosteroid drug that is often used during epidural injections for pain management of mostly spinal pain that could be caused by issues, such as axial degeneration and radiculopathy (2). In instances, such as axial spinal pain and radiculopathy, there is usually inflammation. The inflammatory mediators, such as prostaglandins and phospholipase A2, act to sustain that inflammation leading to pain and discomfort experienced by these patients (2). Corticosteroids, such as dexamethasone, work to inhibit these inflammatory mediators and are effective in reducing the pain that is associated with these conditions, thus making corticosteroids a popular choice for an epidural injection. Corticosteroids are often mixed with local anesthetics, such as lidocaine or bupivacaine, which are an amide class of local anesthetics that also work to reduce the pain. These local

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anesthetics accomplish this reduction in pain by blocking Na+ channels via binding to specific receptors on inner portions of the channel. Together, this mix of a local anesthetic and corticosteroid is common for chronic pain management and treatment. Although effective in treating chronic pain, it is worthwhile to highlight the rare incidence of developing severe hiccups as an adverse effect of dexamethasone administration. As such, we herein report a patient who presented with a rare case of severe hiccups lasting nearly 18 hours after a lumbar medial branch block consisting of dexamethasone and bupivacaine, which resolved spontaneously without any intervention.

CASE

A 59-year-old Caucasian man came to the pain management clinic with complaints of localized pain in his lower back. The patient has a history of spondylosis and left-side sciatica. His past medical history was significant for a severe bicycle accident 15 years ago, in which he sustained multiple broken bones and fractured 7 ribs. His lung was punctured at the time of the accident and he suffered a pneumothorax. Since then, he has a history of spasms on the left side of his chest. An electromyogram was performed at the time of his injuries and it indicated nerve damage on left side of chest, as well as finding decreased strength in his left leg.

Upon arrival to our clinic, he was demonstrating low back pain in the L3-S1 lumbar spinal level. He was given an epidural on the right side and left side of his back, which consisted of 10 mg dexamethasone and 1 mL bupivacaine. The next day, the patient experienced some hiccups as soon as he woke up, but had full resolution shortly after. Seven days later, he returned to our office to receive another set of epidural injections. He was given 10 mg dexamethasone and 1 mL bupivacaine once again on both the right and left side. Shortly after leaving the office, he began having severe hiccups. Toward the end of the night, the hiccups got progressively worse and he was experiencing bad abdominal pain with what he associated as a feeling of gaseous buildup. Although no nausea, he had self-induced vomiting to try and eliminate the acidity in his stomach. The hiccups lasted 18+ hours and were debilitating in nature, severely impacting his ability to eat, drink, and sleep. The next morning, the hiccups were present, but were not as severe as the day prior. He felt bloated and distention in his abdomen. He took some antacids to help relieve the distention and pressure in his abdomen. The hiccups sporadically resolved on the second day, although slight tenderness of the stomach remained for a couple of days. He has had epidurals in the past, about 10 years ago, but has never experienced an adverse effect like this.

Similarly, in Sugandhavesa et al (1), a 49-year-old patient with disc extrusion of L4-S1 causing compression of the S1 nerve root also received 10 mg of dexamethasone in an epidural injection. After the first injection, hiccups occurred but resolved spontaneously on their own within a few hours; however, with every increasing dose, the hiccups got more severe and took longer to resolve. The hiccups seemingly resolved with discontinuation of the medication. The same article describes another case (1) in which a 38-year-old Asian man suffered from severe hiccups for 72 hours after receiving 10 mg of dexamethasone administration for a tonsillectomy.

Research highlighting dexamethasone-induced hiccups (DIH) secondary to epidural treatment is sparse, yet research highlighting DIH secondary to cancer chemotherapy is more copious with more reported incidences. Dexamethasone is an established agent for the prevention of chemotherapy-induced nausea and/or vomiting in both the acute and delayed phases (3). Takiguchi et al (4) cite several reports showing a high incidence of hiccups, i.e., in more than 30% of treated patients during chemotherapy. To determine the frequency of hiccups associated with the use of specific chemotherapeutic agents, Takiguchi et al (4) reviewed database information from various corresponding pharmaceutical companies to assess the prevalence of chemotherapy-induced hiccups, with the hypothesis that it was stemming from dexamethasone use. They found that the total incidence was considerably higher in men (157 of 22,503) than in women (5 of 18,712) ($P < .0001$, chi-square test) (4). Go et al (3) conducted a randomized trial to assess whether the rotation of dexamethasone to methylprednisolone decreases the intensity of DIH in cancer patients treated with chemotherapy. Only men were enrolled in their study and they found that hiccup frequency was 28/33 (84.8%) in the dexamethasone group vs 20/32 (62.5%) in the methylprednisolone group ($P = .04$). Intensity of hiccup was significantly higher in the dexamethasone group than that in the methylprednisolone group (mean NRS-11, 3.5 vs 1.4, $P < .001$) (3). Lee et al (5) also looked to assess the impact of dexamethasone discontinuation and implication of methylprednisolone on DIH. They found that 25

out of 34 patients (73.5%) had recurrence of hiccups after dexamethasone re-administration and compared with baseline values, hiccup intensity (NRS-11: 5.24 vs 2.44) and duration (66.43 minutes vs 22.00 minutes) were significantly attenuated after dexamethasone re-administration (5). Interestingly, of the 40 eligible patients, 38 (95%) were men (5). Cersosimo et al (6) reported a case of a 59-year old man with multiple myeloma who was given high-dose dexamethasone as part of his treatment. It was found that the strong temporal relation between dexamethasone administration and the occurrence of hiccups indicated that dexamethasone was the cause of the patient's hiccups (6).

DISCUSSION

Sciatica is a medical term that refers to pain experienced by patients who have compression of the sciatic nerve, which branches from your lower back through your hips and buttocks and down each leg. Typically, sciatica affects only one side of your body. Sciatica is a common medical complaint. In about 90% of cases (7), sciatica is caused by a herniated disc with nerve root compression, but lumbar stenoses and (less often) tumors are possible causes. In general, an estimated 5%-10% of patients with low back pain have sciatica, whereas the reported lifetime prevalence of low back pain ranges from 49% to 70% (7). Clinical features of sciatica include unilateral leg pain greater than low back pain, pain radiating to foot or toes, numbness and paresthesia in the same distribution, straight leg raising test inducing more leg pain, and localized neurology (11). Sciatica can be diagnosed through history and clinical presentation and can be confirmed via diagnostic imaging, such as magnetic resonance imaging. Depending on severity, sciatica is not always treated by surgical intervention. In fact, surgery seems to be one of the last resort alternatives after many noninvasive forms of treatments have been exhausted first. The most common forms of treatment of sciatica are the usage of nonsteroidal anti-inflammatory drugs, analgesics, and epidurals. Epidurals have increasingly become favorable because although not permanent, do create longer lasting effects. Many patients are able to manage their sciatica symptoms through epidural treatment, and by doing so, they are able to avoid spinal surgery. Epidurals typically include a corticosteroid and a local anesthetic. Given the wide variety of medications to choose within each class, it is often up to the physician's preference to pick the epidural "cocktail." Generally, nonparticulate steroid preparations, such as dexamethasone, are favored for epidural injections due to research indicating its safety (2). In a systematic review, the authors stated that given the lack of strong data favoring the efficacy of one [preparation] over the other, and the potential risk of catastrophic complications, all of which have been with particulate steroids, nonparticulate steroid preparations should be considered as first-line agents when performing epidural steroid injections (ESIs) (8). Several mechanisms leading to the safety risks observed in association with particulate corticosteroid injections have been suggested. The most agreed-upon mechanism is that increased particulate size results in embolization. In in vitro studies, triamcinolone particles were found to be 12 times larger than red blood cells (RBCs), whereas dexamethasone particles were approximately 10 times smaller than RBCs, resulting in less particle aggregation (9). Collectively, review findings suggest nonparticulate corticosteroids, such as dexamethasone, should be the preferred first-line agents when performing cervical or lumbar ESIs. Dexamethasone is a potent anti-inflammatory, analgesic, and antiemetic drug (10). Although generally safe and very effective, high dose and/or chronic use can pose significant risk of developing adverse effects. One rare, but notable adverse effect is that of DIH. DIH is a severe adverse effect that can be seen after dexamethasone use for many different ailments. Although still rare, it has been more common in chemotherapy-related dexamethasone use compared to epidural dexamethasone use; however, both instances of dexamethasone use have had evidence of DIH.

DIH is a male-predominant phenomenon (3-5). Much research has not been implicated in DIH secondary to dexamethasone use in epidurals. However, there have been many reports of high-dose dexamethasone usage in chemotherapy-related emesis, which has led to the onset of severe hiccups. Although it is unclear how this steroid leads to the onset of hiccups, it is known that these steroids have effects on brainstem neurotransmitters and possess other neuroexcitatory properties which are hypothesized and may play a role (11). EPIs were first reported as a pain management therapy in 1930 (12). They have become a popular and effective pain management therapy ever since, especially to relieve lower back pain (13). The injection is named an EPI because it involves injecting a local anesthetic and a steroid medication directly into the epidural space that surrounds the spinal cord and nerve roots (13). Our patient was given 10 mg of dexamethasone and 1 mL of bupivacaine to

help treat his sciatica and its associated low back pain. The combination of dexamethasone and bupivacaine has showed significant effects in treating chronic pain. An et al (14) sought to find the effects of dexamethasone paired with bupivacaine when treating sciatica. They found that dexamethasone added to a clinical concentration of bupivacaine may not only prolong the duration of sensory and motor blockade of sciatic nerve, but also prevent the bupivacaine-induced reversible neurotoxicity and short-term "rebound hyperalgesia" after the resolution of nerve block. Dexamethasone use in chemotherapy has led to many reports of severe hiccups, lasting from hours to days, occurring more frequently in men, and all resolving sporadically on its own (3-6). There has been evidence of chemotherapy-related DIH to resolve with methyl-prednisolone administration and discontinuation of dexamethasone (3,6). However, the rare reported instances of epidural-induced hiccups from dexamethasone administration have also showed a predominance in men, severe episodes lasting hours to days, and sporadically resolving on its own, with little research highlighting alternative ways of resolution (1,10). Further research is needed to test if certain patient populations are more vulnerable or susceptible to developing hiccups, such as those with previous trauma. Further research is also needed to assess the difference in prevalence between DIH in chemotherapy patients vs DIH in epidural patients. Further research is needed to assess the possible synergistic effect on hiccup induction by dexamethasone and other medications. Lastly, further research is needed to see if there is a statistical significance in acute high-dose dexamethasone leading to hiccups vs chronic use of dexamethasone leading to hiccups.

CONCLUSIONS

DIH is a rare, but severe adverse reaction that has been shown to occur in patients who have either acutely used dexamethasone or have been chronically using it. Although hiccups are generally benign and unharmful, DIH have proven to debilitate some patients with its severe effects lasting hours to days. Our patient had gastrointestinal upset that was associated with the severe hiccup reaction, which led to an even more undesirable and enervating experience. There has been some research that has touched upon possible treatments that can be used to diminish DIH; however, most research has suggested that these episodes most commonly resolve on its own. Either way, all of the limited research on this topic has shown that the hiccups progressively get severe over a course of time. Thus, it is imperative to inform your patients of this potential adverse effect ahead of time to ensure that they do not underestimate the onset of the hiccups, which could initially begin as a harmless and acute episode and gradually get worse. More research is needed to further examine the causes, risk factors, and the different type of DIH. It is also important for future research to consider the possible drug-to-drug interactions that may enhance dexamethasone's effect on hiccup induction.

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